PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: lactose monohydrate 90 mg.

3. PHARMACEUTICAL FORM

Film coated tablets.

Blue capsule shaped, film-coated tablets, debossed with 'H' on one side and '124' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- TENOBINE is indicated for the treatment of HIV-1 infection in adults, in combination with other antiretroviral medicines (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors).
- TENOBINE is indicated, in combination with safe sex practices for pre-exposure prophylaxis (PrEP), in adults who are proven to be HIV-1 seronegative; in order to reduce the risk of sexually acquired HIV-1 in adults at high risk, provided maximum treatment compliance is adhered to and can be monitored.

4.2 Posology and method of administration

Posology

Dosage in adults for treatment of HIV-1 infection

The recommended dose is one tablet of TENOBINE (emtricitabine 200 mg and tenofovir DF 300 mg) taken once daily with or without food.

Dosage for PrEP

The recommended dose for HIV-1 uninfected adults is one tablet of TENOBINE (emtricitabine 200 mg and tenofovir DF 300 mg) taken once daily with or without food.

Special population

Dose adjustment for renal impairment

Significantly increased exposure occurred when emtricitabine (200 mg) or tenofovir were administered to patients with moderate to severe renal impairment (see section 4.3).

All individuals should undergo regular monitoring for creatinine clearance and serum phosphorus (see section 4.3 and 4.4).

Paediatric population

Safety and efficacy in patients less than 18 years of age have not been established.

Method of administration

TENOBINE is taken orally with or without food.

4.3 Contraindications

- TENOBINE is contraindicated in patients with known hypersensitivity to emtricitabine, tenofovir, or any of the excipients of TENOBINE (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Moderate to severe renal impairment.
- Creatinine clearance less than 60 ml/min for the PrEP indication.
- Creatinine clearance less than 50 ml/min for HIV-1 treatment indication.
- Safety and efficacy in paediatric patients less than 18 years of age have not been established.
- Co-administration with other tenofovir or emtricitabine containing medicines.
- Co-administration with lamivudine-containing medicines due to similarities between emtricitabine and lamivudine.
- Pre-exposure prophylaxis (PrEP) in subjects who have an unknown or seropositive HIV-1 status.
- In PrEP subjects who are not fully committed to complying with the treatment.

4.4 Special warnings and precautions for use

WARNINGS:

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

TENOBINE IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HBV INFECTION. THE SAFETY AND EFFICACY OF TENOBINE HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV.

IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HAVE DISCONTINUED TENOBINE, 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 TENOBINE IS DISCONTINUED. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

WHEN TENOBINE IS USED FOR PRE-EXPOSURE PROPHYLAXIS (PrEP), PATIENTS MUST BE CONFIRMED TO BE HIV-NEGATIVE IMMEDIATELY BEFORE STARTING AND AT LEAST EVERY 3 MONTHS DURING USE OF TENOBINE.

IF EXISTING HIV-1 INFECTION IS NOT DIAGNOSED AND TENOBINE IS USED FOR PRE-EXPOSURE PROPHYLAXIS (PrEP), RESISTANT STRAINS OF HIV-1 MAY DEVELOP. THEREFORE, DO NOT START TENOBINE FOR PrEP INDICATION IF THE PATIENT HAS ANY SIGNS OR SYPMPTOMS OF HIV-1 INFECTION, UNLESS A SERONEGATIVE RESULT IS CONFIRMED.

The effect of TENOBINE on the clinical progression of HIV-1 has not been studied.

TENOBINE should not be used as a component of a triple nucleoside regimen.

For the PrEP indication, individuals must be warned that full compliance with the treatment is essential to the efficacy in preventing HIV-1 transmission. These individuals must also be educated about other prevention measures, such as condoms. If an individual is not completely committed or cannot be trusted to be fully treatment-compliant, then he/she should not use TENOBINE for PrEP.

Lactic acidosis and severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of TENOBINE alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues such as TENOBINE 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 TENOBINE should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Lactic acidosis/hyperlactataemia

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

- Lactate 2 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 NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, e.g., sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

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

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

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

Mitochondrial dysfunction

Nucleoside and nucleotide analogues such as in TENOBINE have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or 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 TENOBINE, 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 patients receiving TENOBINE. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of TENOBINE until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment

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

Liver disease

Use of TENOBINE can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of TENOBINE has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines. 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 TENOBINE in patients with hepatic impairment (see sections 4.2). Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy, including TENOBINE and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

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

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of TENOBINE.

TENOBINE is not indicated for the treatment of chronic HBV infection and the safety and efficacy of TENOBINE have not been established in patients co-infected with HBV and HIV.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV).

The safety and efficacy of TENOBINE 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 package inserts for these medicines. Tenofovir disoproxil is indicated for the treatment of HBV and emtricitabine has shown activity against HBV in pharmacodynamic studies but the safety and efficacy of TENOBINE have not been specifically established in patients with chronic HBV infection. It is recommended that all patients should be tested for the presence of hepatitis B infection before treatment with TENOBINE. Patients co-infected with HIV and HBV who discontinue TENOBINE should be closely monitored with both clinical and laboratory follow-up for several months after stopping treatment for signs of exacerbations of hepatitis. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Discontinuation of TENOBINE therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Bone mineral density

Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as contained in TENOBINE. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia. TENOBINE 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. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not

studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

Renal impairment in adults

TENOBINE is primarily eliminated by the kidneys by a combination of glomerular filtration and active tubular secretion. TENOBINE should not be administered to HIV-infected patients with creatinine clearance < 30 ml/min or patients requiring haemodialysis. For the PrEP indication, patients with a creatinine clearance < 60 ml/min should not be administered TENOBINE (see section 4.3). If there is a decrease in creatinine clearance in patients using TENOBINE for PrEP, the possible cause should be evaluated and the risks versus benefits should be re-assessed. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir. TENOBINE should be avoided with concurrent or recent use of a nephrotoxic medicine.

Renal monitoring

Prior to initiating TENOBINE for the treatment of HIV-1 infection or for use in pre-exposure prophylaxis, it is recommended that creatinine clearance is calculated in all individuals. In individuals without risk factors for renal disease, it is recommended that renal function (creatinine clearance and serum phosphate) is monitored after two to four weeks of use, after three months of use and every three to six months thereafter. In individuals at risk for renal disease more frequent monitoring of renal function is required. 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.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with TENOBINE.

Renal management in HIV-1 infected patients

If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 50 mL/min in any patient receiving TENOBINE, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Consideration should be given to interrupting treatment with TENOBINE in patients with creatinine clearance decreased to

< 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with TENOBINE should also be considered in case of progressive decline of renal function when no other cause has been identified. Renal safety with TENOBINE has only been studied to a very limited degree in HIV-1 infected patients with impaired renal function (creatinine clearance < 80 mL/min). Dose interval adjustments are recommended for HIV-1 infected patients with creatinine clearance 30-49 mL/min (see section 4.2). Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Furthermore, in a small clinical study, a subgroup of patients with creatinine clearance between 50 and 60 mL/min who received tenofovir disoproxil in combination with emtricitabine every 24 hours had a 2-4-fold higher exposure to tenofovir and worsening of renal function. Therefore, a careful benefit risk assessment is needed when TENOBINE is used in patients with creatinine clearance < 60 mL/min, and renal function should be closely monitored. In addition, the clinical response to treatment should be closely monitored in patients receiving TENOBINE at a prolonged dosing interval. The use of TENOBINE is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in patients who require haemodialysis since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2).

Renal management in pre-exposure prophylaxis

TENOBINE has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population. If serum phosphate is < 1,5 mg/dL (0,48 mmol/L) or creatinine clearance is decreased to < 60 mL/min in any individual receiving TENOBINE for pre-exposure prophylaxis, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Consideration should be given to interrupting use of TENOBINE in individuals with creatinine clearance decreased to
< 60 mL/min or decreases in serum phosphate to < 1,0 mg/dL (0,32 mmol/L). Interrupting use of TENOBINE should also be considered in case of progressive decline of renal function when no other cause has been identified.

Renal monitoring

Renal function (creatinine clearance and serum phosphate) should be evaluated prior to initiating TENOBINE for treatment of HIV-1 or for pre-exposure prophylaxis, and should be monitored during use as in adults (see above).

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. 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.

Co-administration of other medicinal products

TENOBINE should not be used with other medicines that contain emtricitabine or tenofovir (see section 4.3). Emtricitabine and lamivudine are very similar, and therefore should not be used together, including combination lamivudine medicines (see section 4.3).

Didanosine

Concurrent administration of TENOBINE with didanosine should be undertaken with caution. TENOBINE increase the plasma concentrations of didanosine.

Didanosine should be discontinued in patients who develop didanosine-associated adverse events. When TENOBINE and a didanosine enteric-coated formulation are used concomitantly, they can be taken under fasting conditions or with a light meal. When TENOBINE and a didanosine buffered tablet formulation are used concomitantly, they should be taken under fasting conditions.

Nephrotoxic medicines

As TENOBINE is primarily renally eliminated, concurrent administration of TENOBINE with nephrotoxic medicines or other medicines eliminated via active tubular secretion is not recommended (see section 4.5). Examples of such medicines include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir and valganciclovir.

NSAIDs

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 TENOBINE 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.

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.

Atazanavir and lopinavir-ritonavir combination

Concentrations of tenofovir are increased when administered with atazanavir and lopinavir-ritonavir combination. TENOBINE should be discontinued in patients who develop TENOBINE associated adverse events. Atazanavir without ritonavir should not be co-administered with TENOBINE.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing

antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts.
Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, atypical mycobacterial infection, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART) including with TENOBINE. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

HIV-infected patients should be observed for evidence of bone abnormalities, and bone monitoring should be considered for patients with a history of bone fractures or those at risk of osteopenia. Supplementation with calcium and vitamin D may be beneficial for all patients.

Clinical trials that were conducted for the PrEP indication (in HIV-1 uninfected adults) also observed decrease in bone mineral density (BMD). One of the trials found mean change from -0,4 % to - 1,0 % across total hip, spine, femoral neck, and trochanter in the group taking a medicine equivalent to TENOBINE compared to the placebo group. Slightly (although almost insignificantly) more bone fractures were reported in the groups taking TENOBINE than in the placebo group. No correlation between BMD and fractures were noted. Osteomalacia (associated with proximal renal tubulopathy) has been reported with the use of tenofovir DF (as present in TENOBINE) (see section 4.8).

Opportunistic infections

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

The risk of HIV transmission to others

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

Risk of resistance with undetected HIV-1 infection

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

Importance of adherence

The effectiveness of TENOBINE 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 TENOBINE daily dosing schedule.

Comprehensive management to reduce the risk of acquiring HIV-1

The risk of acquisition of HIV-1 is not excluded when taking TENOBINE.

TENOBINE must be used as part of a comprehensive prevention strategy which includes other preventative measures including safe sex.

- Subjects who intend to use TENOBINE as Pre-exposure prophylaxis should be

counselled on safe sex practices, including constant and correct use of condoms; knowledge of their HIV-1 status and their partner's; and they should be advised about regular testing for other sexually transmitted infections (such as syphilis and gonorrhoea) that facilitate the transmission of HIV-1.

- Inform these uninfected adults about and support their efforts to reduce their sexual risk behaviour.

TENOBINE must be used for pre-exposure prophylaxis only in patients who are confirmed to be HIV-negative.

If an HIV-1 infection goes undetected, an individual taking only TENOBINE may develop HIV-1 resistance substitutions since TENOBINE by itself is not a complete treatment regime for HIV-1 infection. It is therefore critical to avoid exposure to TENOBINE in HIV-infected persons (see section 4.3).

- **Many tests for HIV-1, including rapid tests, during the acute stage of infection, detect only anti-HIV antibodies and not the virus itself. Before starting TENOBINE for the PrEP indication, seronegative patients need to be evaluated for signs and symptoms of acute viral infection (such as fever, fatigue, myalgia, etc.) and should be asked about possible exposure events (such as unprotected sex, or a broken condom with an HIV-1 positive partner) that may have occurred within the previous month.**
- **If the patient has signs and symptoms of an acute viral infection or has been potentially exposed to HIV-1 in the past month, initiating TENOBINE should be postponed for at least one month, at which point their HIV status should be confirmed.**
- **During the use of TENOBINE for the PrEP indication, HIV-1 screening tests should be conducted at least every 3 months. If an individual experiences symptoms consistent with an acute viral infection after a potential exposure event, TENOBINE should be discontinued until a negative infection status is confirmed.**

Uninfected patients using TENOBINE for PrEP should be counselled to strictly comply with the dosing schedule. The effectiveness of TENOBINE in reducing the risk of acquiring HIV-1 is strongly correlated with full compliance to the dosage regime.

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 agents. Therefore, the same problems may be seen if TENOBINE is administered with a third nucleoside analogue.

Early virologic failure

Clinical trials in HIV-1 infected patients have shown that regimens that contain three NRTIs are generally less effective than regimens that contain two NRTIs in combination with either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside (NRTIs) regimes are therefore generally not recommended.

Paediatric use

Safety and effectiveness in paediatric patients less than 18 years of age have not been established.

Geriatric use

In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy.

Lactose warning

TENOBINE contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take TENOBINE.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

- Interaction studies have only been conducted in adults taking TENOBINE.

- As TENOBINE contains emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with TENOBINE. Interaction studies have only been performed in adults.
- The steady state pharmacokinetics of emtricitabine and tenofovir have been found to be unaffected when administered together (such as in TENOBINE) versus each medicine used individually.
- Other pharmacokinetic interaction studies have shown that the potential for CYP450 mediated interactions associated with emtricitabine and tenofovir with other medicines is low.

Concomitant use not recommended

- TENOBINE should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide or other cytidine analogues, such as lamivudine (see section 4.4). TENOBINE should not be administered concomitantly with adefovir dipivoxil.
- *Didanosine*: The co-administration of TENOBINE and didanosine is not recommended (see section 4.4 and Table below).
- *Renally eliminated medicinal products:* Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TENOBINE with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.
- TENOBINE is eliminated by active tubular secretion; therefore the use of nephrotoxic medicines or other medicines eliminated by active tubular secretion is not recommended. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4) and if such use is unavoidable, renal function must be monitored.
- The serum concentration of those medicines eliminated by active tubular secretion or TENOBINE may be increased.
- Any interactions that have been identified with emtricitabine and tenofovir individually may occur with TENOBINE. As TENOBINE is a combination of emtricitabine and tenofovir, it should not be co-administered with either tenofovir or emtricitabine individually.
- The interactions listed below should not be considered exhaustive but are representative of the classes of medicines where caution should be exercised.

- Zidovudine: co-administration of zidovudine and emtricitabine resulted in elevation of zidovudine C_{max} as well as AUC.
- Indinavir: no clinically significant medicines interactions have been observed with emtricitabine; however concurrent administration of indinavir and tenofovir resulted in an increase of tenofovir C_{max} and a decrease in indinavir C_{max}.
- Abacavir: co-administration of abacavir and tenofovir resulted in an increase of C_{max} of abacavir.
- It is recommended that atazanavir be administered with ritonavir, atazanavir without ritonavir should not be administered with TENOBINE.
- Saquinavir/ritonavir: co-administration of saquinavir/ritonavir combination with tenofovir DF resulted in an increased C_{min} of tenofovir; as well as increases to the C_{max}, AUC and C_{min} of saquinavir and increased C_{min} of ritonavir.
- Acylovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir or valganciclovir: concurrent administration of TENOBINE and these medicines or medicines that are renally eliminated may increase serum concentrations of emtricitabine, tenofovir or the concurrently administered medicine due to competition for this elimination pathway.
- Oral contraceptives: although no change to the pharmacokinetics of oral contraceptives when taken with TENOBINE were found, a barrier form of contraception should be taken to avoid pregnancy while taking TENOBINE.

Other interactions

Interactions between TENOBINE or its individual component(s) and other medicinal products are listed in Table below (increase in indicated as " ↑ " , decrease as " ↓ " , no change as " ↔ " , twice daily as " b.i.d." and once daily as " q.d."). If available, 90 % confidence intervals are shown in parentheses.

Table: Interactions between TENOBINE or its individual component(s) and other medicinal products

Medicinal product by therapeutic areas	**Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with 90 % confidence intervals if available**	**Recommendation concerning co administration with TENOBINE (emtricitabine 200 mg, tenofovir disoproxil 245 mg)**

	(mechanism)	
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir/Ritonavir/ Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Atazanavir: AUC: ↓ 25 % (↓ 42 to ↓ 3) C_{max}: ↓ 28 % (↓ 50 to ↑ 5) C_{min}: ↓ 26 % (↓ 46 to ↑ 10) Tenofovir: AUC: ↑ 37 % C_{max}: ↑ 34 % C_{min}: ↑ 29 %	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Atazanavir/Ritonavir/ Emtricitabine	Interaction not studied.	
Darunavir/Ritonavir/ Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Darunavir: AUC: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 22 % C_{min}: ↑ 37 %	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir/ Emtricitabine	Interaction not studied.	
Lopinavir/Ritonavir/ Tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d/245 mg q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32 % (↑ 25 to ↑ 38) C_{max}: ↔ C_{min}: ↑ 51 % (↑ 37 to ↑ 66)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).

Lopinavir/Ritonavir/Emtricitabine	Interaction not studied.	
NRTIs		
Didanosine/Tenofovir disoproxil	Co-administration of tenofovir disoproxil and didanosine results in a 40-60 % increase in systemic exposure to didanosine.	Co-administration of TENOBINE and didanosine is not recommended (see section 4.4). Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD_4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.
Didanosine/Emtricitabine	Interaction not studied.	
Lamivudine/Tenofovir disoproxil	Lamivudine: AUC: ↓ 3 % (↓ 8 % to ↑ 15) C_{max}: ↓ 24 % (↓ 44 to ↓ 12) C_{min}: NC Tenofovir: AUC: ↓ 4 % (↓ 15 to ↑ 8)	Lamivudine and TENOBINE should not be administered concomitantly (see section 4.4).

	C_{max}: ↑ 102 % (↓ 96 to ↑ 108) C_{min}: NC	
Efavirenz/Tenofovir disoproxil	Efavirenz: AUC: ↓ 4 % (↓ 7 to ↓ 1) C_{max}: ↓ 4 % (↓ 9 to ↑ 2) C_{min}: NC Tenofovir: AUC: ↓ 1 % (↓ 8 to ↑ 6) C_{max}: ↑ 7 % (↓ 6 to ↑ 22) C_{min}: NC	No dose adjustment of efavirenz is required.
ANTI-INFECTIVES		
Hepatitis B virus (HBV) antiviral agents		
Adefovir dipivoxil/Tenofovir disoproxil	Adefovir dipivoxil: AUC: ↓ 11 % (↓ 14 to ↓ 7) C_{max}: ↓ 7 % (↓ 13 to ↓ 0) C_{min}: NC Tenofovir: AUC: ↓ 2 % (↓ 5 to ↑ 0) C_{max}: ↓ 1 % (↓ 7 to ↑ 6) C_{min}: NC	Adefovir dipivoxil and TENOBINE should not be administered concomitantly (see section 4.4).
Hepatitis C virus (HCV) antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↑ 96 % (↑ 74 to ↑ 121) C_{max}: ↑ 68 % (↑ 54 to ↑ 84) C_{min}: ↑ 118 % (↑ 91 to ↑ 150) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-3310072: AUC: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g.

	C_{max}: ↔ C_{min}: ↑ 42 % (↑ 34 to ↑ 49) Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 63 % (↑ 45 to ↑ 84) Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 45 % (↑ 27 to ↑ 64) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 47 % (↑ 37 to ↑ 58) C_{min}: ↑ 47 % (↑ 38 to ↑ 57)	ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↓ 27 % (↓ 35 to ↓ 18) C_{max}: ↓ 37 % (↓ 48 to ↓ 25) GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal

	Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 48 % (↑ 34 to ↑ 63) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50 % (↑ 42 to ↑ 59) C_{max}: ↑ 64 % (↑ 54 to ↑ 74) C_{min}: ↑ 59 % (↑ 49 to ↑ 70)	monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/ Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓ 34 % (↓ 41 to ↓ 25) C_{max}: ↓ 34 % (↓ 41 to ↑ 25) C_{min}: ↓ 34 % (↓ 43 to ↑ 24) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir:	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

	AUC: ↑ 98 % (↑ 77 to ↑ 123) C_{max}: ↑ 79 % (↑ 56 to ↑ 104) C_{min}: ↑ 163 % (↑ 137 to ↑ 197)	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40 % (↑ 31 to ↑ 50) C_{max}: ↔ C_{min}: ↑ 91 % (↑ 74 to ↑ 110)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Dolutegravir (50 mg q.d.) +	Sofosbuvir: AUC: ↔ C_{max}: ↔	No dose adjustment is required. The increased exposure of tenofovir could potentiate adverse

Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	GS-3310072 AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Dolutegravir AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 65 % (↑ 59 to ↑ 71) C_{max}: ↑ 61 % (↑ 51 to ↑ 72) C_{min}: ↑ 115 % (↑ 105 to ↑ 126)	reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42 % (↑ 37 to ↑ 49) Velpatasvir: AUC: ↑ 142 % (↑ 123 to ↑ 164) C_{max}: ↑ 55 % (↑ 41 to ↑ 71)	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g.

	C_{min}: ↑ 301 % (↑ 257 to ↑ 350) Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 39 % (↑ 20 to ↑ 61) Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 29 % (↑ 15 to ↑ 44) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 55 % (↑ 43 to ↑ 68) C_{min}: ↑ 39 % (↑ 31 to ↑ 48)	ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓ 28 % (↓ 34 to ↓ 20) C_{max}: ↓ 38 % (↓ 46 to ↓ 29) GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 24 % (↓ 35 to ↓ 11) C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/ velpatasvir and darunavir/ ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

	Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39 % (↑ 33 to ↑ 44) C_{max}: ↑ 55 % (↑ 45 to ↑ 66) C_{min}: ↑ 52 % (↑ 45 to ↑ 59)	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Lopinavir/Ritonavir (800 mg/200 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓ 29 % (↓ 36 to ↓ 22) C_{max}: ↓ 41 % (↓ 51 to ↓ 29) GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 30 % (↓ 41 to ↓ 17) C^{min}: ↑ 63 % (↑ 43 to ↑ 85) Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine:	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

	AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 42 % (↑ 27 to ↑ 57) C_{min}: ↔	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Raltegravir (400 mg b.i.d) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Raltegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 21 % (↓ 58 to ↑ 48) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40 % (↑ 34 to ↑ 45) C_{max}: ↑ 46 % (↑ 39 to ↑ 54) C_{min}: ↑ 70 % (↑ 61 to ↑ 79)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Te	Sofosbuvir: AUC: ↔ C_{max}: ↑ 38 % (↑ 14 to ↑ 67)	Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma

nofovir disoproxil (600 mg/200 mg/245 mg q.d.)	GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↓ 53 % (↓ 61 to ↓ 43) C_{max}: ↓ 47 % (↓ 57 to ↓ 36) C_{min}: ↓ 57 % (↓ 64 to ↓ 48) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 81 % (↑ 68 to ↑ 94) C_{max}: ↑ 77 % (↑ 53 to ↑ 104) C_{min}: ↑ 121 % (↑ 100 to ↑ 143)	concentrations of velpatasvir. Coadministration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

	C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40 % (↑ 34 to ↑ 46) C_{max}: ↑ 44 % (↑ 33 to ↑ 55) C_{min}: ↑ 84 % (↑ 76 to ↑ 92)	
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg q.d.)[3] + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 30 % C_{min}: N/A GS-3310072: AUC: ↔ C_{max}: ↔ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC: ↑ 143 % C_{max}: ↑ 72 % C_{min}: ↑ 300 % Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 34 %	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/ velpatasvir /voxilaprevir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

	Ritonavir: AUC: ↑ 45 % C_{max}: ↑ 60 % C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39 % C_{max}: ↑ 48 % C_{min}: ↑ 47 %	
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19 % (↓ 40 to ↑ 10) GS-3310072: AUC: ↔ C_{max}: ↓ 23 % (↓ 30 to ↑ 16) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25 % (↑ 8 to ↑ 45) C_{min}: ↔	No dose adjustment is required.
Ribavirin/Tenofovir disoproxil	Ribavirin: AUC: ↑ 26 % (↑ 20 to ↑ 32) C_{max}: ↓ 5 % (↓ 11 to ↑ 1)	No dose adjustment of ribavirin is required.

	C_{min}: NC	
Herpes virus antiviral agents		
Famciclovir/Emtricitabine	Famciclovir: AUC: ↓ 9 % (↓ 16 to ↓ 1) C_{max}: ↓ 7 % (↓ 22 to ↑ 11) C_{min}: NC Emtricitabine: AUC: ↓ 7 % (↓ 13 to ↓ 1) C_{max}: ↓ 11 % (↓ 20 to ↑ 1) C_{min}: NC	No dose adjustment of famciclovir is required.
Antimycobacterials		
Rifampicin/Tenofovir disoproxil	Tenofovir: AUC: ↓ 12 % (↓ 16 to ↓ 8) C_{max}: ↓ 16 % (↓ 22 to ↓ 10) C_{min}: ↓ 15 % (↓ 12 to ↓ 9)	No dose adjustment is required.
ORAL CONTRACEPTIVES		
Norgestimate/Ethinyl oestradiol/Tenofovir disoproxil	Norgestimate: AUC: ↓ 4 % (↓ 32 to ↑ 34) C_{max}: ↓ 5 % (↓ 27 to ↑ 24) C_{min}: NC Ethinyl oestradiol: AUC: ↓ 4 % (↓ 9 to ↑ 0) C_{max}: ↓ 6 % (↓ 13 to ↑ 0) C_{min}: ↓ 2 % (↓ 9 to ↑ 6)	No dose adjustment of norgestimate/ethinyl oestradiol is required.
IMMUNOSUPPRESSANTS		
Tacrolimus/Tenofovir disoproxil/Emtricitabine	Tacrolimus: AUC: ↑ 4 % (↓ 3 to ↑ 11) C_{max}: ↑ 3 % (↓ 3 to ↑ 9) C_{min}: NC Emtricitabine: AUC: ↓ 5 % (↓ 9 to ↓ 1) C_{max}: ↓ 11 % (↓ 17 to ↓ 5) C_{min}: NC	No dose adjustment of tacrolimus is required.

	Tenofovir: AUC: ↑ 6 % (↓ 1 to ↑ 13) C_{max}: ↑ 13 % (↑ 1 to ↑ 27) C_{min}: NC	
NARCOTIC ANALGESICS		
Methadone/Tenofovir disoproxil	Methadone: AUC: ↑ 5 % (↓ 2 to ↑ 13) C_{max}: ↑ 5 % (↓ 3 to ↑ 14) C_{min}: NC	No dose adjustment of methadone is required.

NC = not calculated.

N/A = not applicable.

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

[2] The predominant circulating metabolite of sofosbuvir.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

A reliable method of contraception should be used to prevent pregnancy.

Pregnancy

Safety in pregnancy has not been established (see section 4.3)

No adequate and well-controlled studies have been done in pregnant women. TENOBINE should not be used in pregnancy (see section 4.3)

Breastfeeding

Safety in lactation has not been established (see section 4.3)

Studies conducted in rats have shown that tenofovir is secreted in breast milk. It is not known if tenofovir and/or emtricitabine are excreted in human milk.

Mothers taking TENOBINE should not breastfeed their infants, because of the potential serious adverse reactions in nursing infants.

Fertility

No human data on the effect of TENOBINE are available.

4.7 Effects on ability to drive and use machines

No studies evaluating the effects of TENOBINE on the ability to drive and use machines have been conducted. However, dizziness is a side effect of both emtricitabine and tenofovir DF, and this may affect the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

a. Summary of safety profile

HIV-1 infection: The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil were nausea (12 %) and diarrhoea (7 %) in an open-label randomised clinical study in adults. The safety profile of emtricitabine and tenofovir disoproxil in this study was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.

Pre-exposure prophylaxis: No new adverse reactions to TENOBINE were identified from two randomised placebo-controlled studies (iPrEx, Partners PrEP) in which HIV-1 uninfected adults received TENOBINE once daily for pre-exposure prophylaxis. Patients were followed for a median of 71 weeks and 87 weeks, respectively. The most frequent adverse reaction reported in the TENOBINE group in the iPrEx study was headache (1 %).

Any adverse events that have been identified with emtricitabine and tenofovir individually may occur with TENOBINE.

b. Tabulated summary of adverse reactions

Side-effects which have been associated with the individual components of TENOBINE are listed below:

Frequency	**Emtricitabine**	**Tenofovir disoproxil fumarate**
Blood and lymphatic system disorders		
Frequent:	Neutropenia	
Less frequent:	Anaemia	Neutropenia, haematuria.
Immune system disorders		
Frequent:	Allergic reaction	

Less frequent:	Angioedema	Angioedema
Frequency unknown		Allergy
Metabolism and nutrition disorders		
Frequent:	Hyperglycaemia, hypertriglyceridaemia	Hypophosphataemia
Less frequent:		Hypokalaemia
Frequency unknown:	Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with nucleoside reverse transcriptase inhibitors.	Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with nucleoside reverse transcriptase inhibitors. Hypertriglyceridaemia, hyperglycaemia.
Psychiatric disorders		
Frequent:	sleep disturbances (insomnia, abnormal dreams), depressive disorder.	
Frequency unknown:	Neuropathy, paraesthesia, peripheral neuritis, asthenia.	Depression, asthenia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety.
Nervous system disorders		
Frequent:	Headache, dizziness	Headache, dizziness
Respiratory, thoracic and mediastinal disorders		
Less frequent:	Increased cough and rhinitis	Chest pain, pneumonia, dyspnoea
Gastrointestinal disorders		
Frequent:	Diarrhoea, nausea, elevated amylase, including elevated pancreatic amylase, elevated	diarrhoea, vomiting, nausea, abdominal pain, flatulence,

	serum lipase elevation, vomiting, abdominal pain, dyspepsia	abdominal distension, dyspepsia, anorexia
Less frequent:	Abdominal pain	Pancreatitis, serum-amylase concentrations may be raised
Hepatobiliary disorders		
Frequent:	Hyperbilirubinaemia, elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT)	Increased liver enzymes (including increased AST, increased ALT and/or gamma GT)
Less frequent:		Hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders		
Frequent:	Vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration	
Less frequent:	Skin discolouration manifested by hyperpigmentation on the palms and/or sole, but is generally mild	Skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash)
Musculoskeletal, connective tissue and bone disorders		
Frequent:		Bone density decreased (see section 4.4)
Less frequent:		Myopathy, osteomalacia (both associated with proximal renal tubulopathy)

		(manifested as bone pain and infrequently contributing to fractures), rhabdomyolysis, muscular weakness
Frequency unknown	Myalgia, arthralgia	Back pain, myalgia, arthralgia
Renal and urinary disorders		
Frequent:	Elevated creatinine kinase	
Less frequent:		Increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome, renal failure, (acute and chronic, acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus, polyuria
General disorders and administration site conditions		
Frequent:	Pain, asthenia	Asthenia, fever, sweating, weight loss

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

If overdose occurs the patients must be monitored for toxicity, including monitoring of vital signs and observation of the patient's clinical status and standard supportive measures must be applied (see section 4.8). There is limited clinical experience of acute overdosage with

TENOBINE. In overdose, side effects will be exacerbated and exaggerated. Contact a poison control centre for further management of overdose or unintentional ingestion.
Treatment of an overdose is essentially symptomatic and supportive.
To enhance elimination of emtricitabine and tenofovir, haemodialysis is used.

Emtricitabine
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) is removed by haemodialysis treatment. Removal of emtricitabine by peritoneal dialysis has not been established.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents.
Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations.
ATC Code: J05AR03

TENOBINE is a combination of 2 antiretroviral agents, viz. emtricitabine and tenofovir disoproxil fumarate which are nucleoside reverse transcriptase inhibitors (NRTI's).

Mechanism of action

Emtricitabine and tenofovir disoproxil fumarate

Combination studies that evaluated the *in vitro* antiviral activity of emtricitabine and tenofovir together, demonstrated synergistic effects.

PROFESSIONAL INFORMATION

Emtricitabine

Emtricitabine is a synthetic nucleoside analogue cytidine. Emtricitabine enters the cells by passive diffusion and is phosphorylated by cellular enzymes to form to its active metabolite, emtricitabine 5'-triphosphate. The intracellular emtricitabine 5' -triphosphate acts as a competitive inhibitor of HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine-5'-triphosphate and is incorporated into nascent viral DNA to cause chain termination. Emtricitabine has a low affinity for human DNA polymerase α, β, ε and mitochondrial DNA polymerase γ and has therefore low toxicity to the host.

Tenofovir disoproxil fumarate

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 hydrolysed to tenofovir, and then undergoes phosphorylation by cellular kinases to form tenofovir diphosphate, the active metabolite. Tenofovir diphosphate is a competitive inhibitor of viral reverse transcriptases (HIV-1 RT) by competing with the natural substrate deoxyadenosine 5'-triphosphate. It is incorporated into HIV DNA to cause chain termination due to its incomplete ribose ring. Although tenofovir diphosphate has a broad spectrum of activity against viral DNA polymerases, it has low affinity for human DNA polymerases - α, β and y, which is the basis for its selective toxicity.

Resistance and cross-resistance

Combination emtricitabine and tenofovir disoproxil fumarate:

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been detected in cell culture. Genotypic analysis of these isolates found the M184I/V and/or K65R amino acid substitutions in the viral reverse transcriptase (RT) enzyme.

Cross resistance has been observed in some of the nucleoside reverse transcriptase inhibitors (NRTIs). The M184V/I and/or K65R amino acid substitutions that are found in the cell cultures of combination emtricitabine and tenofovir treated patients, have also been identified in some HIV-1 isolates from individuals failing treatment with tenofovir in combination with emtricitabine. Thus, it has been shown that cross-resistance among these NRTIs may possibly occur in patients whose virus has either one or both of these amino acid substitutions.

Emtricitabine

High level resistance to emtricitabine occurs with the mutation of methionine to valine substitution at codon 184(M184V). The K65R mutation confers resistance to emtricitabine and other cytosine analogues.

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral medicines. In a clinical study, viral isolates from 6/16 (37,5 %) treatment-naïve patients with virologic 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.

In terms of cross-resistance; emtricitabine-resistant isolates (M184V/I) were shown to be cross-resistant to lamivudine and zalcitabine, but seemed to retain susceptibility (*in vitro*) to didanosine, stavudine, tenofovir, zidovudine and NNRTIs. *In vivo* studies with abacavir, didanosine, tenofovir and zalcitabine containing the K65R amino acid substitution, showed reduced susceptibility to inhibition by emtricitabine. Viruses containing mutations which cause reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V), have not been found to be resistant to emtricitabine.

Tenofovir disoproxil fumarate

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 2 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. Multinucleoside resistant HIV-1 with a T68S double insertion mutation in the RT has been shown to have reduced susceptibility to tenofovir.

Efavirenz 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.

Resistance in terms of the Pre-exposure prophylaxis (PrEP) indication

In a clinical study for pre-exposure prophylaxis, heterosexual couples (of whom one of the partners was infected with HIV-1) were studied and were separated into three groups. One group was taking emtricitabine and tenofovir DF combination, the second group was taking tenofovir DF, and the third group was taking placebo.

At the time of seroconversion, none of the subjects (infected with HIV-1 during the trial) had developed amino acid substitution associated with emtricitabine and tenofovir resistance.

In a clinical study of HIV-1 seronegative men who have sex with men were involved and were divided into two groups. One group was taking emtricitabine and tenofovir DF combination, and the other group was taking placebo.

At the time of seroconversion, none of the subjects (infected with HIV-1 during the trial) had developed amino acid substitution associated with emtricitabine and tenofovir resistance.
At enrolment time, 10 subjects were found to already be infected with HIV-1; 3 of these 10 subjects had the M184V/I substitutions associated with resistance to emtricitabine. Two out of 3 of these subjects were in the emtricitabine and tenofovir DF combination group. One subject (emtricitabine/tenofovir DF group) had a wild type virus and developed the M184V substitution 4 weeks after enrolment; and the other subject had indeterminate resistance, and 4 weeks after enrolment was found to have the M184I substitution.

5.2 Pharmacokinetic properties

Emtricitabine

Absorption: Emtricitabine has an oral bioavailability of 93 % and is rapidly absorbed with peak plasma concentrations occurring at 1-2 hours post dose. The AUC is not affected by food, while C_{max} is reduced by food, emtricitabine can however be taken without regard to food.

Protein binding: *In vitro* binding of Emtricitabine to human plasma proteins is less than 4 % and is independent of concentration over the range of 0,02 to 200 µg/ml. Following administration of radio-labelled 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.

Elimination: Emtricitabine is excreted primarily unchanged in the urine, undergoing glomerular filtration and active tubular secretion. Relative to other nucleoside analogues, emtricitabine has a slow systemic clearance and a long elimination half-life of 8 to 10 hours. In addition, the estimated half-life of the intracellular triphosphate is very long (up to 39 hours) therefore affording the rationale for a once-daily dosing of this agent.

Tenofovir disoproxil fumarate

Absorption: 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. Subsequent to oral administration of tenofovir maximum serum concentrations (C_{max}) were achieved in 1,0 ± 0,4 hours.

Protein binding: *In vitro* Plasma protein binding of tenofovir is less than 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/ml.

Elimination: The terminal elimination half-life of single oral dose of tenofovir is approximately 17 hours; the intracellular elimination half-life of tenofovir triphosphate is 11 to 49 hours. This is the reason once-daily dosing is possible. Tenofovir is eliminated by both glomerular filtration and active tubular secretion; 70 to 80 % of an intravenous dose of tenofovir is eliminated unchanged in the urine. In patients with renal insufficiency, doses should be decreased.

Effects of food on oral absorption

The combination tablet may be administered with or without food. The time to tenofovir C_{max} was delayed by approximately 0,75 hours following administration of the combination tablet with a high fat meal or a light meal. 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

Paediatric and geriatric patients

The pharmacokinetics of emtricitabine and tenofovir DF have not been evaluated in children (< 8 years weighing < 35 kg) or in the elderly (> 65 years) (see section 4.4).

Patients with renal impairment

Renal impairment has been found to affect the pharmacokinetics of emtricitabine and tenofovir (see section 4.3 and 4.4). In patients with a creatinine clearance of less than 50 ml/min, the C_{max} and AUC0-∞ of emtricitabine and tenofovir were increased significantly. It is therefore recommended that TENOBINE should not be used in patients with a creatinine clearance of less than 30 ml/min, or in patients with end-stage renal disease who are on dialysis (see section 4.3 and 4.4).

TENOBINE should not be used for the PrEP indication in patients who have a creatinine clearance of less than 60 ml/min (see section 4.3 and 4.4).

Patients with hepatic impairment

The pharmacokinetics of tenofovir after a 300 mg dose of tenofovir DF was studied in non-HIV infected subjects with moderate to severe hepatic impairment; this study showed no significant difference in the tenofovir pharmacokinetics in the subjects with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine or emtricitabine/tenofovir DF combination has not been studied in subjects with hepatic impairment. However, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment on the pharmacokinetics of emtricitabine is expected to be limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose
Pregelatinised starch
Lactose monohydrate (Pharmatose 200M)

Coating excipients:
Opadry II Blue (coating)

Opadry II Blue contains: hypromellose 15 Cp, FD&C blue #2/ indigo carmine aluminium lake, lactose monohydrate, titanium dioxide (CI 77891), Triacetin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

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, 30, 56 or 60 tablets are packed in a white, opaque HDPE container with a white, ribbed plastic closure with continued threading with a pulp liner.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No information available.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
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Midrand
1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER

TENOBINE: 44/20.2.8/0837

DATE OF APPROVAL: 23 JULY 2025

PROFESSIONAL INFORMATION

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 15 April 2011

10. DATE OF REVISION OF THE TEXT

23 July 2025

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PI 32075 06/2025

DATE OF APPROVAL: 23 JULY 2025