APPROVED PROFESSIONAL INFORMATION FOR TEERENZ

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TEERENZ 600 mg/200 mg/300 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg equivalent to 245 mg of tenofovir disoproxil.

Excipient with known effect

Contains sugar: lactose monohydrate 129 mg. For full list of excipients, see section 6.1

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

TEERENZ IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TEERENZ HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE OR TENOFOVIR, WHICH ARE COMPONENTS OF TEERENZ. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH-BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE CO-INFECTED WITH HIV AND HBV AND DISCONTINUE TEERENZ. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

3 PHARMACEUTICAL FORM

Blue coloured capsule-shaped, biconvex film-coated tablets engraved TEE on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TEERENZ is indicated for use alone as a complete regimen or in combination with other anti-retroviral medicines for the treatment of HIV-1 infection in adults.

4.2 Posology and method of administration

TEERENZ therapy should be initiated by a medical practitioner experienced in the management of human immunodeficiency virus (HIV) infection.

Posology

Adults: The dose of **TEERENZ** is one tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Paediatrics: TEERENZ is not recommended for use in patients younger than 18 years of age.

Renal impairment: Because **TEERENZ** is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance < 50 ml/min).

Hepatic impairment: The pharmacokinetics of **TEERENZ** have not been studied in patients with hepatic impairment. Patients with mild liver disease (Child-Pugh-Turcotte (CPT), Class A) may be treated with the normal recommended dose of **TEERENZ** (see sections 4.3, 4.4 and 5.2). Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz (see sections 4.3 and 4.4). If **TEERENZ** is discontinued in patients co-infected with HIV, these patients must be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Dose adjustment: If **TEERENZ** is co-administered with rifampicin to patients weighing 50 kg or more, an additional 200 mg/day (800 mg total) of efavirenz may be considered (see section 4.5).

A dose reduction and therapeutic drug monitoring should be considered in patients weighing

less than 40 kg and presenting with long-term neuropsychiatric effects such as ataxia, encephalopathy, hyper-somnolence and coma.

Method of administration

TEERENZ should be taken once daily, orally without food

4.3 Contraindications

- **TEERENZ** is contraindicated in patients with previously demonstrated hypersensitivity to tenofovir, disoproxil, emtricitabine, efavirenz or to any of the excipients of **TEERENZ** listed in section 6.1.
- **TEERENZ** should not be administered concurrently with terfenadine, astemizole, bepridil, cisapride, midazolam, pimozide, triazolam or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g. cardiac arrhythmias, prolonged sedation or respiratory depression).
- **TEERENZ** should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see section 4.5).
- Co-administration with herbal preparations containing St. John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).
- **TEERENZ** is contraindicated in patients with moderate to severe renal impairment (creatinine clearance less than 50 ml/min) and in patients with a history of previous liver injury/failure with efavirenz-containing antiretroviral treatment (ART).
- Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other anti-retrovirals.

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 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 **TEERENZ** 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).

Routine testing of serum lactate levels in asymptomatic patients on anti-retrovirals is not recommended. Measurement of serum lactate levels is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis.

Lactic acidosis/hyperlactataemia

Use of **TEERENZ** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/l) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/l with minimum symptoms: switch to agents that are less likely to cause lactic acidosis, monitor regularly, and be alert for clinical signs
- Lactate 5-10 mmol/l without symptoms: monitor closely.
- Lactate 5-10 mmol/l with symptoms and/or with reduced standard bicarbonate: STOP all therapy 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, lymphoma and hyperthyroidism.
- Lactate greater than or equal to 10 mmol/l: STOP all therapy (80 % mortality in case studies).

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

Caution should be exercised when administering **TEERENZ** to patients with known risk factors

for liver disease.

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

Mitochondrial dysfunction

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

Pancreatitis

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

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **TEERENZ** 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 **TEERENZ** is increased due to decreased clearance. The dose of **TEERENZ** should therefore be adjusted (see section 4.2).

Liver disease

Use of **TEERENZ** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic

steatosis). The safety and efficacy of **TEERENZ** 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 professional information for these medicines. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

There is some evidence that efavirenz is associated with three clinical pathological patterns of drug induced liver failure in HIV positive patients of which the sub massive necrosis histological pattern seems to be associated with a high morbidity/mortality risk and may present many months after therapy has been initiated or even stopped. Risk factors include younger age, CD4 + counts ≥ 350 cells/microliters and female gender.

Patients on **TEERENZ** or efavirenz containing ART should be regularly monitored for jaundice (including a laboratory bilirubin and liver enzymes) and bleeding tendencies.

Early detection and treatment of liver failure and the immediate discontinuation of **TEERENZ** or efavirenz containing medicines should be stressed. Patients who discontinued treatment with **TEERENZ** should be followed up for symptoms/signs of liver failure for up to 12 months.

TEERENZ is not recommended in patients with moderate to severe impairment because there are insufficient data to determine whether dose adjustments are required.

Patients Co-infected with HIV and hepatitis B (HBV) or C

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines.

It is recommended that all patients with HIV be tested for the presence of chronic HBV before initiating anti-retroviral therapy. **TEERENZ** is not indicated for the treatment of chronic HBV infection and the safety and efficacy of **TEERENZ** have not been established in patients co-

infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued emtricitabine or tenofovir. In some of these patients treated with emtricitabine, the exacerbations of hepatis B were associated with liver decompensation and liver failure. Hepatic function should be monitored closely with both clinical and laboratory follow up for at least several months in patients who are co-infected with HIV and HBV and discontinue **TEERENZ**. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. If appropriate, initiation of anti-hepatitis B therapy may be warranted. Discontinuation of **TEERENZ** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Co-administration with related medicines

Related medicines not for co-administration with **TEERENZ** include emtricitabine, tenofovir, emtricitabine/tenofovir and efavirenz, which contain the same active components as **TEERENZ**. Due to similarities between emtricitabine and lamivudine, **TEERENZ** should not be co-administered with medicines containing lamivudine, including lamivudine/zidovudine, lamivudine, abacavir/lamivudine or abacavir/lamivudine/ zidovudine.

Medicine interactions (see section 4.5)

Concomitant use of **TEERENZ** and St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products is not recommended. Co-administration of NNRTIs, including efavirenz, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz leading to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

Psychiatric symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1 008 patients treated with regimens containing efavirenz for a mean of 2,1 years and 635 patients treated with control regimens for a mean of 1,5 years, the frequency of

specific serious psychiatric events among patients who received efavirenz or control regimens, respectively were: severe depression (2,4 %, 0,9 %) suicidal ideation (0,7 %, 0,3 %), nonfatal suicide attempts (0,5 %, 0 %), aggressive behaviour (0,4 %, 0,5 %), paranoid reactions (0,4 %, 0,3 %) and manic reactions (0,2 %, 0,3 %). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study AI26006 (006), treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection medicine use, psychiatric history and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control- treated patients. One percent of efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional post-marketing reports of death by suicide, delusions and psychosis-like behaviour, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see section 4.8).

TEERENZ may cause long-term neuropsychiatric effects.

Severe reversible ataxia, often with signs of encephalopathy, associated with supra- therapeutic efavirenz concentrations were reported in underweight women (less than 40 kg) who were probably slow metabolisers.

Cases of efavirenz-induced hyper-somnolence resulting in coma and death and brain histology demonstrated by vacuolar axonopathy were reported.

Lower doses of **TEERENZ** and therapeutic drug monitoring should be considered in patients with body weight of less than 40 kg and patients presenting with severe and prolonged neuropsychiatric manifestations.

Nervous system symptoms

Fifty-three percent of patients receiving efavirenz in controlled trials reported central nervous system symptoms compared to 25 % of patients receiving control regimens. These symptoms included dizziness (28,1 %), insomnia (16,3 %), impaired concentration (8,3 %), somnolence (7,0 %), abnormal dreams (6,2 %) and hallucinations (1,2 %). Other reported symptoms were euphoria confusion, agitation, amnesia, stupor, abnormal thinking and depersonalisation. The majority of these symptoms were mild-moderate (50,7 %); symptoms were severe in 2,0 % of patients. Overall, 2,1 % of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5 % to 9 % in patients treated with regimens containing efavirenz and from 3 % to 5 % in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms (see section 4.4). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see section 4.8 and section 4.2).

Analysis of long-term data from Study 006, (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with efavirenz + zidovudine + lamivudine, efavirenz + indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the indinavir-containing control arm.

Patients receiving **TEERENZ** should be alerted to the potential for additive central nervous system effects when **TEERENZ** is used concomitantly with alcohol or psychoactive medicines.

Renal impairment (see section 4.3)

Emtricitabine and tenofovir are principally eliminated by the kidneys, however efavirenz is not. Since **TEERENZ** is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance less than 50 ml/min should not receive **TEERENZ**.

$$\text{CrCl (ml/min)} = \frac{\text{140-age (years) x weight (kg) [0,85 if female]}}{\text{72 x serum creatinine (mgdl)}}$$

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported in association with the use of tenofovir.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with **TEERENZ**. Routine monitoring of calculated creatinine clearance and serum phosphorous should be performed in patients at risk for renal impairment.

TEERENZ should be avoided with concurrent or recent use of a nephrotoxic medicine.

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

Reproductive risk potential

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving **TEERENZ**. Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other, hormonal contraceptive). Women of childbearing potential should undergo pregnancy testing before initiation of **TEERENZ**. If this medicine is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking **TEERENZ**, the patient should be apprised of the potential harm to the foetus.

There are no adequate and well-controlled studies of **TEERENZ** in pregnant women.

Efavirenz

From reports received by the anti-retroviral Pregnancy Register, 322 pregnancies were exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (316

pregnancies). Birth defects occurred in 6 of 255 live births (first-trimester exposure) and 1 of 17 live births (second/third trimester exposure). None of these prospectively reported defects were neural tube defects. However, there have been four retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies in efavirenz.

Paediatric use

TEERENZ is not recommended for patients less than 18 years of age because it is a fixed-dose combination tablet containing a component, tenofovir, for which safety and efficacy have not been established in this age group.

Elderly use

Sufficient studies have not been performed on subjects aged 65 and over to determine whether they respond differently from younger subjects. 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.

Skin Rash

In controlled clinical trials, 26 % of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17 % of patients treated in control groups. Rash associated with blistering, moist desquamation or ulceration occurred in 0,9 % of patients treated with efavirenz. The incidence of Grade 4 rash (e.g. erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0,1 %. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1,7 %.

TEERENZ can be reinitiated in patients interrupting therapy because of rash. **TEERENZ** should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Experience with efavirenz in patients who discontinued other anti-retroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz and two of these patients discontinued because of rash.

Liver Enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended (see section 4.4). In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with **TEERENZ** needs to be weighed against the unknown risks of significant liver toxicity (see section 4.8).

Because of the extensive cytochrome P450 mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering **TEERENZ** to these patients.

Bone Effects

In a 144-week study of treatment naïve patients, decreases in bone mineral density (BMO) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir DF + lamivudine + efavirenz compared with patients receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the study and this reduction was sustained through 144 weeks. Twenty-eight percent of tenofovir DF treated patients versus 21 % of the comparator patients lost at least 5 % of BMD

at the spine or 7 % of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir DF group and 6 patients in the comparator group. Tenofovir DF was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 vitamin D levels were also higher in patients receiving tenofovir DF. The effects of tenofovir DF associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the tenofovir DF professional information.

Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir DF (see section 4.8).

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.

Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Caution must be taken in any patient with a history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolised by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels (see section 4.5).

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. 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 anti-retroviral therapy and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, *Mycobacterium avium* infection, atypical mycobacterial infections, cytomegalovirus, *Pneumocystis jirovecii (carinii)* pneumonia (PCP) and cryptococcal meningitis, which may necessitate further evaluation and treatment.

Appropriate treatment of the opportunistic disease should be instituted or continued, and anti-retroviral therapy 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. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving **TEERENZ** 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 **TEERENZ**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Concomitant use of *Ginkgo biloba* extracts is not recommended (see section 4.5)

Lactose

TEERENZ contains lactose and should not be taken by patients with rare hereditary problems, or a history of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicines and other forms of interaction

Efavirenz: Efavirenz has been shown *in vivo* induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with medicines primarily metabolised by these isozymes may result in altered plasma concentrations of the co-administered medicine. Therefore, appropriate dose adjustments may be necessary for these medicines.

Medicines which induce CYP3A4 activity (e.g. phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Efavirenz exposure may be increased when given with medicines (for example ritonavir) or food

(for example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example *Ginkgo biloba* extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz.

Emtricitabine and tenofovir DF: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of **TEERENZ** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir and/or other renally eliminated medicines. Some examples included, but are not limited to, aciclovir, adefovir dipivoxil, cidofovir, ganciclovir, valaciclovir and valganciclovir.

Co-administration of tenofovir DF 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.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving either atazanavir or lopinavir/ritonavir with tenofovir DF should be monitored for tenofovir-associated adverse events. **TEERENZ** should be discontinued in patients who develop tenofovir-associated adverse events.

Medicines that are contraindicated or not recommended for use with TEERENZ

Antifungal

Voriconazole: Efavirenz significantly decreases voriconazole plasma concentrations and co-administration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz associated side effects.

Antihistamine

Astemizole, terfenadine: Due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

Anti-migraine

Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methyl-ergonovine): Due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.

Anti-retrovirals

Efavirenz, emtricitabine, tenofovir DF, lamivudine: Not for use with **TEERENZ** because the active ingredients - emtricitabine/tenofovir DF and efavirenz are components of **TEERENZ**. Lamivudine is similar to emtricitabine.

Benzodiazepines

Midazolam, triazolam: Due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Calcium channel blocker

Bepridil: Due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

GI motility agent

Cisapride: Due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

Neuroleptic

Pimozide: Due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

St. John's wort (*Hypericum perforatum*): Expected to substantially decrease plasma levels of efavirenz; but it has not been studied in combination with efavirenz.

Established and other potentially significant medicine interactions: Alteration in dose or regimen may be recommended based on medicine interaction studies or predicted interaction

Anti-retroviral agents:

Protease inhibitor:

Amprenavir*:* Efavirenz has the potential to decrease serum concentrations of amprenavir.

***Fosamprenavir calcium**:* Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and **TEERENZ** with respect to safety and efficacy have not been established.

Fosamprenavir/ritonavir: An additional 100mg/day (300 mg total) of ritonavir is recommended when **TEERENZ** is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when **TEERENZ** is administered with fosamprenavir plus ritonavir twice daily.

***Atazanavir**:* Plasma concentrations of atazanavir were decreased by both efavirenz and tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with **TEERENZ**. Therefore, co-administration of **TEERENZ** and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations.

***Indinavir**:* The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1 000 mg every 8 hours does not compensate for ~~tile~~ the increased indinavir metabolism due to efavirenz.

***Lopinavir/ritonavir**:* A dose increase of lopinavir/ritonavir to 600 mg/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Patients should be monitored for tenofovir associated adverse events. **TEERENZ** should be discontinued in patients who develop tenofovir-associated adverse events.

***Ritonavir**:* When ritonavir 500 mg every 12 hours was co-administered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g. dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when **TEERENZ** is used in combination with ritonavir.

***Saquinavir**:* Should not be used as sole protease inhibitor in combination with **TEERENZ**.

NRTI:

***Didanosine**:* Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. In adults weighing more than 60 kg, the didanosine dose should be reduced to 250 mg if co-administered with **TEERENZ**. Data are not available to recommend a dose adjustment of didanosine for patients weighing less than 60 kg.

When co-administered, **TEERENZ** and didanosine may be taken under fasted conditions or with a light meal (less than 400 kcal, 20 % fat). Co-administration of didanosine buffered formulation with **TEERENZ** should be under fasted conditions. Co-administration of **TEERENZ** and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. For additional information, please consult the didanosine professional information.

Other medicines:

Anticoagulant

Warfarin: Plasma concentrations and effects potentially increased or decreased by efavirenz.

Anticonvulsants

Carbamazepine: There are insufficient data to make a dose recommendation for **TEERENZ**. Alternative anticonvulsant treatment should be used.

Phenytoin, phenobarbital (phenobarbitone): Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.

Vigabatrin and gabapentin: Can be co-administrated with **TEERENZ** without dose adjustment.

Antidepressant

Sertraline: Increases in sertraline dose should be guided by clinical response. **Paroxetine:** Can be co-administrated with **TEERENZ** without dose adjustment. () **Fluoxetine:** Can be co-administrated with **TEERENZ** without dose adjustment. () ***Antifungals***

Itraconazole: Since no dose recommendation for itraconazole can be made, alternative treatment should be considered.

Ketoconazole: Medicine interaction studies with **TEERENZ** and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.

Anti-infective

Clarithromycin: Clinical significance unknown. In uninfected volunteers, 46 % developed rash while receiving efavirenz and clarithromycin. No dose adjustment of **TEERENZ** is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be

considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with **TEERENZ**.

Antimycobacterial

Rifabutin: Increase daily dose of rifabutin by 50 %. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.

Rifampicin: When **TEERENZ** is taken with rifampicin in patients weighing 50 kg or greater, an additional 200 mg/day (800 mg total) of efavirenz may provide exposure similar to a daily efavirenz dose of 600 mg when taken without rifampicin. The clinical effect of this dose adjustment has not been adequately evaluated.

Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2). No dose adjustment of rifampicin is recommended when given with **TEERENZ**.

Calcium channel blockers

Diltiazem: Dose adjustments should be guided by clinical response (refer to the complete professional information for diltiazem). No dose adjustment of **TEERENZ** is necessary when administered with diltiazem.

Others (e.g. felodipine, nicardipine, nifedipine, verapamil): No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the complete professional information for the calcium channel blocker).

HMG-CoA

Atorvastatin, pravastatin, simvastatin: Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased with efavirenz. Consult the complete professional information for the HMG-CoA reductase inhibitor for guidance on individualising the dose.

Narcotic analgesic

Methadone: Co-administration of efavirenz in HIV-infected individuals with a history of injection medicine use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms. Patients

should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Oral contraceptive

Ethinylestradiol: Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception should be used in addition to oral contraceptives.

Efavirenz assay interference

Cannabinoid test interaction: Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics Cedia DAU Multi-level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

Other interactions

Efavirenz

Medicine interaction studies were performed with efavirenz and other medicines likely to be co-administered or medicines commonly used as probes for pharmacokinetic interaction. There was no clinically significant interaction observed between efavirenz and zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine or paroxetine. Single doses of famotidine or an aluminium and magnesium antacid with simethicone had no effects on efavirenz exposures.

Emtricitabine and tenofovir disoproxil fumarate

No clinically significant medicine interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir DF and zidovudine. Similarly, no clinically significant medicine interactions have been observed between tenofovir DF and abacavir, adefovir dipivoxil, efavirenz, emtricitabine, indinavir lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin and saquinavir/ritonavir in studies conducted in healthy volunteers. Following multiple dosing to HIV-negative subjects receiving either chronic methadone

maintenance therapy, oral contraceptives or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a rack of clinically significant medicine interactions between these agents and tenofovir DF.

Nephrotoxic medicines: Use of **TEERENZ** should be avoided with concurrent or recent use of a nephrotoxic medicines. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

CCR5 antagonists: No effect is suspected when maraviroc is co-administrated with **TEERENZ**. Refer to the maraviroc professional information.

Integrase strand transfer inhibitor: Raltegravir can be co-administrated with **TEERENZ** without dose adjustment.

Immunosuppressants: Decreased exposure of immunosuppressants metabolised by CYP3A4 (e.g. ciclosporin, tacrolimus, sirolimus) may be expected due to CYP3A4 induction. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least two weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with **TEERENZ**.

Norepinephrine and dopamine reuptake inhibitors: Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz. ()

Co-administration with related medicines

Related medicines not for co-administration with **TEERENZ** include emtricitabine, tenofovir, emtricitabine/tenofovir and efavirenz, which contain the same active components as **TEERENZ**. Due to similarities between emtricitabine and lamivudine, **TEERENZ** should not be co-administered

with medicines containing lamivudine, including lamivudine/ zidovudine, lamivudine, abacavir/lamivudine or abacavir/lamivudine/zidovudine.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential /Contraception in males and females

Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives) while on therapy with **TEERENZ.** Because of the long half-life of efavirenz, the use of adequate contraceptive measures for 12 weeks after discontinuation of **TEERENZ** is recommended.

Women of childbearing potential should have a medically and/or laboratory supervised pregnancy test before initiation of **TEERENZ.** This test should be repeated at frequent intervals during treatment to exclude pregnancy.

Pregnancy

TEERENZ should not be used in pregnancy.

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving **TEERENZ**. If **TEERENZ** is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking **TEERENZ,** the patient should be informed of the potential harm to the foetus. A small number of cases of neural tube defects, including meningomyelocele, have been reported but causality has not been established. Late onset neurological disorders relating to mitochondrial dysfunction have been observed in children who have been exposed *in utero* and/or postnatally to nucleoside analogues as contained in **TEERENZ**.

There are no adequate and well-controlled studies of **TEERENZ** in pregnant women.

If a patient becomes pregnant while taking **TEERENZ** the patient (and partner) should be counselled and informed about the potential harm to the foetus. The possibility of termination of pregnancy should be considered and discussed with both patients if there is already evidence

of severe harm to the foetus. If termination is unavoidable the patient should be treated with an alternative medicine, known to be safe or safer for use in pregnancy. If no safe or safer alternative is available, cannot be tolerated, has failed or is contraindicated, both partners should be counselled and written consent preferable to both partners be obtained to continue treatment with **TEERENZ**.

If a patient is to be treated with **TEERENZ**, pregnancy should be excluded 24 hours prior to initiation of treatment.

Breastfeeding

It is recommended that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that both efavirenz and tenofovir are secreted in milk. Efavirenz, emtricitabine and tenofovir have been shown to be excreted in human milk.

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

Fertility

No human data on the effect of **TEERENZ** on fertility are available. Animal studies do not indicate harmful effects on efavirenz, emtricitabine or tenofovir on fertility.

4.7 Effects on ability to drive and use machines

TEERENZ may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms, they should avoid potentially hazardous tasks such as driving or operating machinery when they are on **TEERENZ**.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Efavirenz

MedDRA system organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Less frequent	Hypersensitivity
	Frequency unknown	Immuno-allergic liver injury/failure.
Metabolism and nutrition disorders	Less frequent	Hypertriglyceridaemia, hypercholesterolaemia
Psychiatric disorders	Frequent	Depression, anxiety, abnormal dreams, insomnia
	Less frequent	Suicide attempt, suicide ideation, psychosis, mania, paranoia, hallucination, euphoric mood, affect lability, confusional state, aggression, completed suicide, delusion, neurosis
	Frequency unknown	Ataxia, hyper-somnolence, encephalopathy and coma
Nervous system disorders:	Frequent	Cerebellar coordination and balance disturbances, somnolence, headache, disturbance in attention, dizziness
	Less frequent	Convulsions, amnesia, thinking abnormal, ataxia, coordination abnormal, agitation, tremor
Eye disorders	Less frequent	Blurred vision
Ear and labyrinth disorders	Less frequent	Tinnitus, vertigo
Cardiac disorders	Frequency unknown	Palpitations and tachycardia
Vascular disorders	Less frequent	Flushing
Respiratory system disorders	Frequency unknown	Respiratory depression (when co-

MedDRA system organ class	Frequency	Adverse reactions
		administered with medicines competing for cytochrome P450 (CYP)3A4)
Gastrointestinal disorders:	Frequent	Diarrhoea, vomiting, abdominal pain, nausea
	Less frequent	Pancreatitis
Hepatobiliary disorders,	Frequent	Elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated gamma-glutamyltransferase (GGT)
	Less frequent	Hepatitis acute, hepatic failure
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus
	Less frequent	Stevens-Johnson syndrome, erythema multiforme, severe rash, photoallergic dermatitis, acne, alopecia, eczema, folliculitis, seborrhoea, skin exfoliation, urticarial, nail disorders, skin discolouration, maculopapular rash
Musculoskeletal system disorders	Frequency unknown	Arthralgia, myalgia and myopathy
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequent	Fatigue, allergic reaction, asthenia, hot flushes influenza-like symptoms, malaise, syncope

Emtricitabine

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequent	Neutropenia
	Less frequent	Anaemia
Immune system disorders	Frequent	Allergic reaction, angioedema
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia, hypertriglyceridaemia
Psychiatric disorders	Frequent	Abnormal dreams, insomnia
Nervous system disorders	Frequent	Headache, dizziness
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia
Hepatobiliary disorders	Frequent	Elevated serum AST and/or elevated serum ALT, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Frequent	Vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)
Musculoskeletal and connective tissue disorders	Frequent	Elevated creatine kinase
Renal and urinary system disorders	Frequent	Elevation of creatinine
General disorders and administration site conditions	Frequent	Pain, asthenia

Tenofovir disoproxil fumarate

MedDRA system organ class	Frequency	Adverse reactions
Immune system disorders	Frequency	Allergic reactions, angioedema

MedDRA system organ class	**Frequency**	**Adverse reactions**
	unknown	
Metabolism and nutrition disorders	Frequent	Hypophosphataemia
	Less frequent	Hypokalaemia, lactic acidosis, hypertriglyceridaemia, hyperglycaemia
Nervous system disorders	Frequent	Headache, dizziness, peripheral neuropathy
Psychiatric disorders	Frequency unknown	Depression, insomnia and anxiety
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Chest pain, pneumonia, dyspnoea
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
	Less frequent	Pancreatitis, raised serum amylase concentrations, dyspepsia
Hepatobiliary disorders	Frequent	Increased transaminases
	Less frequent	Hepatic steatosis, hepatitis, hepatotoxicity
Skin and subcutaneous tissue disorders	Frequent	Rash (including pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash)
Musculoskeletal and connective tissue disorders	Less frequent	Rhabdomyolysis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy

MedDRA system organ class	Frequency	Adverse reactions
Renal and urinary disorders	Less frequent	Increased creatinine, proteinuria, renal failure (acute and chronic), acute tubular necrosis, proximal renal tubulopathy including Fanconi syndrome, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus
General disorders and administration site conditions	Frequent	Asthenia, fever, sweating, weight loss

Paediatric population: TEERENZ is not recommended for use in patients younger than 18 years of age (see section 4.2).

Patients with renal impairment: Because **TEERENZ** is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

If an overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of the patient's clinical status; standard supportive treatment should then be applied as necessary. Administration of activated charcoal may be

used to aid removal of unabsorbed efavirenz. Haemodialysis can remove both emtricitabine and tenofovir (refer to detailed information below) but is unlikely to significantly remove efavirenz from the blood.

Efavirenz: Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions. **Emtricitabine:** Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology study single doses of emtricitabine 1 200 mg were administered to 11 patients. No severe adverse reactions were reported.

Haemodialysis treatment removes approximately 30 % of the emtricitabine dose over a 3-hour dialysis period starting within 1,5 hours of emtricitabine dosing (blood flow rate of 400 ml/min and a dialysate flow rate of 600 ml/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir disoproxil fumarate: Limited clinical experience at doses higher than the therapeutic dose of tenofovir 300 mg is available. In one study, 600 mg tenofovir was administered to 8 patients orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a 4-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.2.8 Antiviral agents

Pharmacotherapeutic group: Antiviral for systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR06

Mechanism of action and pharmacodynamic effects

TEERENZ is a fixed-dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz is a non-nucleoside reverse transcriptase inhibitor;

emtricitabine is a synthetic nucleoside analogue of cytidine, and tenofovir DF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5' - monophosphate.

Efavirenz: Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ and δ are not inhibited by efavirenz.

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

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

Antiviral Activity

Efavirenz, emtricitabine and tenofovir disoproxil fumarate: In combination studies evaluating the antiviral activity in cell culture of emtricitabine and efavirenz together, efavirenz and tenofovir together and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.

Efavirenz: The concentration of efavirenz inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90 to 95 % (EC_{90-95}) ranged from 1, 7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells and macrophage/monocyte cultures. Efavirenz demonstrated additive antiviral activity against HIV-1 in cell culture when combined with non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine and nevirapine), nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zalcitabine and zidovudine), protease inhibitors (PIs) (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir) and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F G, J and N), but had reduced antiviral activity against group O viruses. Efavirenz is not active against HIV-2.

Emtricitabine: The antiviral activity in cell culture of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50 % effective concentration (EC_{50}) values for emtricitabine were in the range of 0,0013 to 0,64 µM (0,0003 to 0,158 µg/ml). In medicine combination studies of emtricitabine with NRTIs (abacavir, lamivudine, stavudine, zalcitabine and zidovudine), NNRTIs (delavirdine, efavirenz and nevirapine), and PIs (amprenavir, nelfinavir, ritonavir and saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E. F and G (EC_{50} values ranged from 0,007 to 0,075 µM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0,007 to 1,5 µM).

Tenofovir disoproxil fumarate: The antiviral activity in cell culture of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0,04 to 8,5 µM. In medicine combination studies of tenofovir with NRTIs (abacavir, didanosine. lamivudine, stavudine, zalcitabine and zidovudine), NNRTIs (delavirdine,

efavirenz and nevirapine), and PIs (amprenavir, indinavir, nelfinavir, ritonavir and saquinavir), additives to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and 0 (EC_{50} values ranged 0,5 to 2,2 µM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1,6 µM to 4,9 µM).

Resistance

Efavirenz, emtricitabine, and tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In a clinical study of treatment-naïve patients resistance analysis was performed on HIV isolates from all virologic failure patients with more than 400 copies/ml of HIV-1 RNA at week 48 or early discontinuations. Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Resistance to efavirenz occurred in 75 % analysed patients in the emtricitabine + tenofovir DF group and in 73 % analysed patients in the zidovudine/lamivudine fixed-dose combination group. The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 17 % analysed patient isolates in the emtricitabine + tenofovir DF group and in 32 % analysed patient isolates in the zidovudine/lamivudine group. Through 48 weeks, no patients developed a detectable K65R mutation in their HIV as analysed through standard genotypic analysis. Insufficient data are available to assess the development of K65R mutation upon prolonged exposure to this regimen.

In a clinical study of treatment naïve patients, isolates from 8 of 47 patients receiving tenofovir DF developed the K65R substitution through 144 weeks of therapy; 7 of these occurred in the first 48 weeks of treatment and one at Week 96. In treatment experienced patients, 5 % of tenofovir DF treated patients with virologic failure through Week 96 showed more than 1,4-fold (median 2,7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Cross-resistance

Efavirenz, emtricitabine and tenofovir disoproxil fumarate: Cross-resistance profiles for efavirenz, nevirapine and delavirdine *in vitro* demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs.

The potential for cross-resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action. The potential for cross-resistance between efavirenz and PIs is low because of the different enzyme targets involved.

Resistance to emtricitabine or tenofovir has been seen *in vitro* and in some HIV-1 infected patients due to the development of an M184V or M184I substitution in RT with emtricitabine or a K65R substitution in RT with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these medicines plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. Both the K65R and M184V/I mutation remain fully susceptible to efavirenz. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either an M41L or an L210W substitution in RT showed reduced susceptibility to tenofovir disoproxil.

5.2 Pharmacokinetic properties

TEERENZ: One **TEERENZ** tablet is bioequivalent to one 600 mg efavirenz, plus 200 mg emtricitabine plus 300 mg tenofovir DF following single-oral administration to fasting healthy subjects.

Absorption

Efavirenz: In HIV-infected patients time-to-peak plasma concentrations are approximately 3 to 5 hours and steady-state plasma concentrations are reached in 6 to 10 days. In 35 patients

receiving efavirenz 600 mg once daily, steady-state C_{max} was 12,9 ± 3,7 µM (mean ± SD), C_{min} was 5,6 ± 3,2 µM and AUC was 184 ± 73 µM/hr.

Emtricitabine: Following oral administration, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-infected subjects, the steady-state plasma emtricitabine C_{max} was 1,8 ± 0,7 µg/ml (mean ± SD) and the AUC over a 24-hour dosing interval was 10,0 ± 3,1 µg/hr/ml.

Tenofovir disoproxil fumarate: Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1,0 ± 0,4 hours (mean ± SD) and C_{max} and AUC values were 296 ± 90 ng/ml and 2287 ± 685 ng/hr/ml respectively. The oral bioavailability of tenofovir from tenofovir DF in fasted patients is approximately 25 %.

Distribution

Efavirenz: Efavirenz is highly bound to human plasma proteins (99,5 % to 99,75 %), predominantly albumin. Following administration of ^{4}C-labeled efavirenz, 14 to 34 % of the dose was recovered in the urine and 16 to 61 % was recovered in faeces.

Emtricitabine: The mean steady state plasma trough concentration at 24 hours post-dose was 0,09 µg/ml. The mean absolute bioavailability of emtricitabine was 93 %. *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.

Tenofovir disoproxil fumarate: *In vitro* binding of tenofovir to human plasma proteins is less than 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/ml.

Biotransformation

Efavirenz: *In vitro* studies suggest CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in induction of its own metabolism.

Emtricitabine: 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.

Tenofovir disoproxil fumarate: Approximately 70 to 80 % of the intravenous dose of tenofovir is recovered as unchanged medicine in the urine.

Elimination

Efavirenz: Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses.

Emtricitabine: Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 213 ± 89 ml/min (mean ± SD). Following a single oral dose, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate: Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 ml/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of food on oral absorption

TEERENZ has not been evaluated in the presence of food. Administration of efavirenz tablets with a high fat meal increased the mean AUC and C_{max} of efavirenz by 28 % and 79 %, respectively, compared to administration in the fasted state. Compared to fasted administration,

dosing of tenofovir DF and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35 % and 15 %, respectively, without affecting emtricitabine exposures (see sections 4.3, 4.4 and 4.8).

Special Populations

Race

Efavirenz: The pharmacokinetics of efavirenz in patients appears to be similar among the racial groups studied.

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of emtricitabine.

Tenofovir disoproxil fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir DF.

Gender

Efavirenz, emtricitabine and tenofovir disoproxil fumarate: Efavirenz, emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Paediatric and elderly patients

Pharmacokinetic studies of tenofovir DF have not been performed in paediatric patients younger than18 years old. Efavirenz has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg. Emtricitabine has been studied in paediatric patients from 3 months to 17 years of age. **TEERENZ** is not recommended for paediatric administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir have not been fully evaluated in the elderly (more than 65 years) (see sections 4.4 and 4.8).

Patients with Impaired Renal Function

Efavirenz: The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1 % of efavirenz is excreted unchanged in the urine, so the

impact of renal impairment on efavirenz elimination should be minimal.

Emtricitabine and tenofovir disoproxil fumarate: The pharmacokinetics of emtricitabine and tenofovir DF are altered in patients with renal impairment. In patients with creatinine clearance less than 50 ml/min, C_{max} and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased (see sections 4.3 and 4.4).

Patients with Hepatic Impairment

Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see section 4.4).

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

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

5.3 Preclinical safety data

Refer to the individual professional information of tenofovir disoproxil fumarate, emtricitabine and efavirenz.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium

Hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulphate

Film-coating:

Polyethylene glycol

Polyvinyl alcohol

Talc (E553b)

FD & C Blue #2/Indigo carmine aluminium lake (E132)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years when stored at or below 25 ºC.

6.4 Special precautions for storage

Store at or below 25 ºC

Keep the bottle tightly closed.

6.5 Nature and contents of container

A white opaque high-density polypropylene (HDPE) container. The container closure system is child resistant. Each HDPE container contains 28, 30 or 84 tablets; containers are sealed with an induction seal.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma SA (Pty) Ltd

106 16th Road

Building 2

Midrand

8 REGISTRATION NUMBER(S)

50/20.2.8/1047

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 September 2020

10 DATE OF REVISION OF THE TEXT

26 August 2025