PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ATENEF

(efavirenz 600 mg/ emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg)

Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Efavirenz…….600 mg

Emtricitabine…….. 200 mg

Tenofovir disoproxil fumarate …….300 mg

equivalent to Tenofovir disoproxil……...245 mg

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White to off-white, capsule shaped, film-coated tablets debossed with ‘RF21’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults:

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

Special populations

Paediatrics:

ATENEF is not recommended for use in patients less than 18 years of age.

Renal Impairment:

Because **ATENEF** 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 less than 50 ml/min).

Method of Administration

Oral use.

ATENEF tablets should be swallowed whole once daily.

4.3 Contraindications

- Hypersensitivity to efavirenz, emtricitabine, tenofovir disoproxil fumarate or to any of the excipients listed in section 6.1.
- **ATENEF** should not be administered concurrently with 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). It should not be administeredconcurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see section 4.5).
- Pregnancy and lactation seesection 4.6).
- Moderate to severe renal impairment [Creatinine clearance less than 50 ml/min (see **section** 4.4 and section 5.2)].
- Patients with a history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART) (see section 4.4).

4.4 Special warnings and precautions for use

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.

ATENEF is not indicated for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of **ATENEF** has not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued emtricitabine or tenofovir, which are components of ATENEF**.** Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV and HBV and discontinue **ATENEF.** If appropriate, initiation of anti-hepatitis B therapy may be warranted.

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 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 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 ATENEF tablets 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 ART is not recommended. Measurement of serum lactate levels is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis.

Lactate 2 to 5 mmol/l: monitor regularly and be alert for clinical signs.

Lactate 5 to 10 mmol/l without symptoms: monitor closely.

Lactate 5 to 10 mmol/l with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uremia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).

Lactate greater than or equal to 10 mmol/l: STOP all therapy (80 % mortality in case studies).

Patients Co-infected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic HBV before initiating antiretroviral therapy. **ATENEF** tablets are not indicated for the treatment of chronic HBV infection, and the safety and efficacy of **ATENEF** tablets 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 coinfected with HBV and HIV and have discontinued emtricitabine or tenofovir DF. In some of these patients treated with emtricitabine, the exacerbations of hepatitis 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 **ATENEF** tablets. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Co-administration with Related Medicines

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

Medicine Interactions (see section 4.5)

Concomitant use of **ATENEF** and St. John's wort (*Hypericium 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 and may lead to virological response and possibly resistance to efavirenz or to the class of NNRTI's.

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. These include: severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behaviour, paranoid reactions, and manic reactions. Factors associated with an increase in the occurrence of these psychiatric symptoms are a history of injection medicine use, psychiatric history, and receipt of psychiatric medication. Cases of efavirenz-treated patients who discontinued or interrupted treatment because of one or more of

these selected psychiatric symptoms have been reported. There have also been post-marketing reports of death by suicide, delusions, and psychosis-like behavior, 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).

Nervous System Symptoms

These symptoms include dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations. Other reported symptoms are euphoria, confusion, agitation, amnesia, stupor, abnormal thinking, and depersonalisation. Patients should be informed that these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of the less frequent psychiatric symptoms (see section 4.4**,** Psychiatric Symptoms). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see section 4.2 and section 4.6).

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

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

Renal Impairment (see section 4.3)

Emtricitabine and tenofovir are principally eliminated by the kidney; however, efavirenz is not. Since efavirenz, emtricitabine and tenofovir disoproxil fumarate fixed dose tablets is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance below 50 ml/min should not receive **ATENEF**.

$$eCl_{cr}\ (ml/min) = \frac{[140 - age] \times Wt\ (kg) \times 0.85\ (if\ female)}{S_{cr}\ (\mu mol/L)}$$

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 DF (see section 4.8).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with efavirenz, emtricitabine and tenofovir disoproxil fumarate fixed dose combination tablets. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

ATENEF should be avoided with concurrent or recent use of a nephrotoxic agent.

Efavirenz induced liver injury (see section 4.3)

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 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/µl and female gender.

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

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

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

The safety and efficacy of **ATENEF** in patients with both HIV and hepatitis B virus infection have not been established.

Paediatric Use

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

Use in the elderly

Clinical studies of efavirenz, emtricitabine, or tenofovir DF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly 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

New-onset skin rash, rash associated with blistering, moist desquamation, or ulceration may occur in patients treated with efavirenz. These include Grade 4 rash (e.g., erythema multiforme, Stevens-Johnson syndrome). Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz and, in most patients continuing therapy with efavirenz, rash resolves within 1 month. **ATENEF** can be reinitiated in patients interrupting therapy because of rash. **ATENEF** 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.

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, Patients Co-infected With HIV and HBV). In patients with persistent elevations of serum transaminases to greater than five times the ULN, the benefit of continued therapy with **ATENEF** needs to be weighed against the unknown risks of significant liver toxicity (see section 4.8, Laboratory Abnormalities).

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 **ATENEF** to these patients.

Bone Effects

In treatment-naive patients, decreases in bone mineral density (BMD) were seen at the lumbar spine and hip Tenofovir DF is 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 are 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, consult the tenofovir DF package insert.

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 or psychiatric disorders, including depression.

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).

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of **ATENEF** tablets. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii (carinii)* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Opportunistic infections

Patients receiving **ATENEF** may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by medical practitioners experienced in the treatment of patients with associated HIV disease.

The risk of HIV transmission to others

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

Appropriate precautions should continue to be employed.

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. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipidaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient op permanent is not known. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

4.5 Interaction with other medicines and other forms of interaction

Interactions (see also section 4.3 and section 4.4)

Efavirenz: Efavirenz has been shown *in vivo* to induce CYP3A. Other compounds that are substrates of CYP3A 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 that induce CYP3A4 activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Emtricitabine and Tenofovir Disoproxil Fumarate: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of **ATENEF** 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 include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, 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 (for didanosine dosing adjustment recommendations, see Table 3 in section 4.3). Suppression of CD4+ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.

Atazanavir and lopinavir/ritonavir has 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 (and therefore **ATENEF**) should be monitored for tenofovir-associated adverse events (for atazanavir dosing adjustment recommendations, see Table 3 in section 4.3).

Other important medicine interaction information for **ATENEF** is summarised in Table 2 and 3. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential medicine interactions; no medicine interaction studies have been conducted using **ATENEF**. The tables include potentially significant interactions but are not all inclusive.

Table 2

Medicines That Are Contra-indicated or not Recommended for Use With ATENEF

Medicine Class: Medicine Name	**Clinical Comment**
Antifungal: voriconazole	CONTRA-INDICATED because efavirenz significantly decreases voriconazole plasma concentrations, and co-administration may decrease the therapeutic efficacy of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects.

Antihistamine: astemizole	CONTRA-INDICATED due to potential for serious and/ or life-threatening reactions such as cardiac dysrhythmias.
Anti-migraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRA-INDICATED 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 efavirenz, emtricitabine and tenofovir disoproxil fumarate fixed dose combination tablets because the active ingredients- efavirenz, emtricitabine, tenofovir DF are components of ATENEF. Lamivudine is similar to emtricitabine.
Benzodiazepines: midazolam, triazolam	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression
Calcium channel blocker: bepridil	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
GI motility agent: cisapride	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Neuroleptic: pimozide	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
St. John's wort (*Hypericum perforatum*)	NOT RECOMMENDED: Expected to substantially decrease plasma levels of efavirenz: has not been studied in combination with efavirenz.

Table 3

Established and Other Potentially Significant[1] Medicine Interactions: Alteration in Dose or Regimen May Be Recommended Based on Medicine Interaction Studies or Predicted Interaction

Concomitant Medicine Class: Medicine Name	**Effect**	**Clinical Comment**

Protease inhibitor: Amprenavir	↓ amprenavir concentration	Efavirenz has the potential to decrease serum concentrations of amprenavir.
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and **ATENEF** with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when **ATENEF** are administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when **ATENEF** are administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓atazanavir concentration ↑ tenofovir concentration	Plasma concentrations of atazanavir are decreased by both efavirenz and tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with **ATENEF**. Therefore, co-administration of atazanavir and **ATENEF** is not recommended due to concerns regarding decreased atazanavir concentrations.
Protease inhibitor: Indinavir	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 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. ATENEF should be**

		discontinued in patients who develop tenofovir-associated adverse reactions.
Protease inhibitor: Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours is co-administered with efavirenz 600 mg once daily, the combination is associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when **ATENEF** are used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with **ATENEF.**
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. **In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg if co-administered with ATENEF. Data are not available to recommend a dose adjustment of didanosine for patients weighing less than 60 kg.** When co-administered, **ATENEF** 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 **ATENEF** should be under fasted conditions. **Co-administration of ATENEF** 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 package insert.**
Other agents		

Anticoagulant: Warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for **ATENEF.** Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓anticonvulsant concentration ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Antifungals: Itraconazole Ketoconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration ↓ ketoconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered. Medicine interaction studies with **ATENEF** and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Anti-infective: Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46 % developed rash while receiving efavirenz and clarithromycin. No dose adjustment of **ATENEF** 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 **ATENEF.**
Antimycobacterial: Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50 %. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.

Antimycobacterial: Rifampicin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentration is unknown. Dosing recommendations for concomitant use of **ATENEF** and rifampin have not been established.
Calcium channel blockers: Diltiazem Others (e.g. felodipine, nicardipine, nifedipine, verapamil)	↓ diltiazem concentration ↓ desacetyl diltiazem concentration ↓ N-monodesmethy↓ diltiazem concentration ↓ calcium channel blocker	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of **ATENEF** is necessary when administered with diltiazem. No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin concentration	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreases with efavirenz. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualising the dose.
Narcotic analgesic: Methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-1 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 contraceptives: Ethinyl oestradiol	↑ ethinyl oestradiol concentration	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.
1. This table is not all inclusive.		

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. For more information, please consult the efavirenz package insert.

Other Interactions

Efavirenz

Medicine interaction studies were performed with efavirenz and other medicines likely to be coadministered 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 aluminum 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 disoproxil fumarate and zidovudine. Similarly, no clinically significant medicine interactions have been observed between tenofovir disoproxil fumarate 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 lack of clinically significant medicine interactions between these agents and tenofovir disoproxil fumarate.

Immunosuppressants metabolised by CYP3A4 (e.g. ciclosporin, sirolimus)/Efavirenz:

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 **ATENEF**.

4.6 Fertility, pregnancy and lactation

Pregnancy

ATENEF 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 **ATENEF**. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of **ATENEF**. If this medicine is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be appraised of the potential harm to the foetus. Birth defects may occur in live births.

There are no adequate and well-controlled studies of ATENEF.

Breastfeeding

It is recommended that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that both efavirenz and tenofovir are secreted in milk. It is not known whether efavirenz, emtricitabine, or tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving ATENEF**.

Fertility

No human data on the effect of ATENEF are available.

4.7 Effects on ability to drive and use machines

Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

The undesirable effects from clinical study and post-marketing experience with **ATENEF** and the individual components of **ATENEF** in antiretroviral combination therapy are listed in the table below by body system organ class, frequency and the component(s) of **ATENEF** to which the undesirable effects are attributable.

Tabulated list of adverse reactions

	ATENEF		
	Efavirenz	**Emtricitabine**	**Tenofovir disoproxil fumarate**
Blood and lymphatic system disorders:			
Frequent		neutropenia	
Less frequent		anaemia	neutropenia
Immune system disorders:			
Frequent		allergic reaction	allergic reaction
Less frequent	hypersensitivity Immuno- allergic liver injury/failure	angioedema	angioedema
Metabolism and nutrition disorders:			
Frequent		hyperglycaemia, hypertriglycerid-aemia lactic acidosis, usually associated with severe hepatomegaly and steatosis	hypophosphataemia, hyperglycaemia, hypertriglycerid-aemia
Less frequent	raised serum cholesterol and triglycerides		hypokalaemia lactic acidosis, usually associated with severe hepatomegaly and steatosis
Psychiatric disorders:			
Frequent	depression, anxiety, abnormal dreams,insomnia	abnormal dreams, insomnia, depressive disorders	depression

Less frequent	suicide attempt, suicide ideation, psychosis, mania, paranoia, hallucination, euphoric mood, affect lability, confusional state, aggression completed suicide, delusion, neurosis, depersonalisation		
Nervous system disorders:			
Frequent	cerebellar coordination and balance disturbances, somnolence, headache, disturbance in attention, dizziness	headache dizziness	dizziness headache, insomnia, peripheral neuropathy including peripheral neuritis, anxiety
Less frequent	convulsions, amnesia, thinking abnormal, ataxia, coordination abnormal, agitation, tremor, paraesthesia, hypoaesthesia	asthenia, sleep disorders, neuropathy, peripheral neuritis, paraesthesia	
Eye disorders:			
Less frequent	vision blurred		
Ear and labyrinth disorders:			
Less frequent	tinnitus, vertigo		
Cardiac disorders:			
Less frequent	palpitations		
Vascular disorders:			
Less frequent	flushing		
Respiratory, thoracic and mediastinal disorders:			
Frequent	dyspnoea	increased cough, rhinitis	chest pain, pneumonia, dyspnoea

Gastrointestinal disorders:			
Frequent	diarrhoea, vomiting, abdominal pain, nausea anorexia, constipation, malabsorption, dyspepsia	diarrhoea, nausea elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	diarrhoea, vomiting, nausea abdominal pain, abdominal distension, flatulence, raised serum amylase, anorexia, pancreatitis
Less frequent	pancreatitis, raised serum amylase		
Hepatobiliary disorders:			
Frequent	Raised liver enzymes	elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubin-aemia	increased transaminases
Less frequent	hepatitis acute hepatic failure		hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:			
Frequent	rash (moderate-severe, all grades), pruritus	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)	rash (including pruritus, maculopapular rash, urticaria,vesiculo-bullous rash and pustular rash)
Less frequent	Stevens-Johnson syndrome, erythema multiforme, severe rash, photoallergic dermatitis		
Musculoskeletal and connective tissue disorders:			

Frequent	arthralgia, myalgia	elevated creatine kinase	
Less frequent	myopathy	arthralgia, myalgia	rhabdomyolysis, muscular weakness osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy, myalgia, arthralgia
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
Reproductive system and breast disorders:			
Less frequent	gynaecomastia		
General disorders and administration site conditions:			
Frequent	fatigue, asthenia	pain, asthenia	asthenia

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

Symptoms

Efavirenz: 600 mg twice daily have been reported to increase nervous system symptoms.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine.

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

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. 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 DF, a 4-hour hemodialysis session removed approximately 10 % of the administered tenofovir dose.

Treatment

If 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 DF but is unlikely to significantly remove efavirenz from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class & Category: A 20.2.8 Antiviral agents

ATENEF is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF).

Efavirenz: Efavirenz is a non-nucleoside reverse transcriptase inhibitor 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 σ are not inhibited by efavirenz.

Emtricitabine: Emtricitabine is 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 to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of the 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 polymerase 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 90–95 % (EC90-95) ranged from 1,7−25 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 clade B and 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-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50 % effective concentration (EC50) values for emtricitabine were in the range of 0,0013–0,64 µM (0,0003–0,158 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 (EC50 values ranged from 0,007–0,075 µM) and showed strain specific activity against HIV-2 (EC50 values ranged from 0,007–1,5 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 EC50 values for tenofovir were in the range of 0,04–8,5 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), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC50 values ranged from 0,5–2,2 µM) and showed strain specific activity against HIV-2 (EC50 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 trial of treatment-naive patients resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure patients with greater 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 9/12 (75 %) analysed patients in the emtricitabine + tenofovir DF group and in 16/22 (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 2/12 (17 %) analysed subject isolates in the emtricitabine + tenofovir DF group and in 7/22 (32 %) analysed subject isolates in the zidovudine/lamivudine group. Through 48 weeks no patients developed a detectable K65R mutation in their HIV-1 as analysed through standard genotypic analysis. Insufficient data are available to assess the development of the K65R mutation upon prolonged exposure to this regimen.

In a clinical trial of treatment-naive subjects, isolates from 8/47 analysed 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 subjects, 14/304 (5 %) of tenofovir DF treated

subjects with virologic failure through Week 96 showed greater than 1,4 fold (median 2,7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a substitution in the HIV1 RT gene resulting in the K65R amino acid substitution.

Cross-resistance

Efavirenz, Emtricitabine, and Tenofovir disoproxil fumarate: Cross-resistance has been recognised among NNRTIs. Cross-resistance has also been recognised among certain NRTIs. The M184V/I and/or K65R substitutions selected in cell culture 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.

5.2 Pharmacokinetic properties:

Efavirenz: In HIV-1 infected patients time-to-peak plasma concentrations are approximately 3–5 hours and steady-state plasma concentrations are reached in 6–10 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state Cmax was 12,9 ± 3,7 µM (mean ± SD), Cmin was 5,6 ± 3,2 µM, and AUC was 184 ± 73 µM·hr. Efavirenz is highly bound (approximately 99,5–99,75 %) to human plasma proteins, predominantly albumin. Following administration of 14C-labelled efavirenz, 14–34 % of the dose is recovered in the urine (mostly as metabolites) and 16–61 % is recovered in faeces (mostly as parent medicine). In vitro studies suggest CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52–76 hours after single doses and 40–55 hours after multiple doses.

Emtricitabine: Following oral administration, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the steady-state plasma emtricitabine Cmax 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. 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 0,02−200 µg/ml. Following administration of radiolabelled

emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion 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: Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1 infected patients in the fasted state, maximum serum concentrations (Cmax) were achieved in 1,0 ± 0,4 hrs (mean ± SD) and Cmax 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 subjects is approximately 25 %. In vitro binding of tenofovir to human plasma proteins is less than 0,7 % and is independent of concentration over the range of 0,01–25 µg/ml. Approximately 70−80 % of the intravenous dose of tenofovir is recovered as unchanged medicine in the urine. 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

Efavirenz, emtricitabine and tenofovir disoproxil fumarate fixed dose combination tablet has not been evaluated in the presence of food. Administration of efavirenz tablets with a high fat meal increased the mean AUC and Cmax 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 Cmax of tenofovir by 35 % and 15 %, respectively, without affecting emtricitabine exposures.

Special Populations

Paediatric and Elderly Patients

Pharmacokinetic studies of tenofovir DF have not been performed in paediatric patients (less than 18 years). 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. Efavirenz, emtricitabine and tenofovir disoproxil fumarate fixed dose combination tablet 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 section 4.4).

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 below 50 ml/min, Cmax and AUC0-∞ of emtricitabine and tenofovir were increased (see section 4.3 and section 4.4, Renal Impairment).

Patients with Hepatic Impairment

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Croscarmellose sodium

Iron oxide red

Magnesium stearate

Hydroxypropyl cellulose

Sodium lauryl sulfate

Film coat:

Polyvinyl Alcohol – Part. hydrolysed

Titanium Dioxide

Macrogol/PEG 3350

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C in the original package, protected from moisture.

6.5 Nature and contents of container

28, 30, 84 or 90 Tablets packed in a white opaque HDPE bottle. The HDPE bottle is packed with or without an outer cardboard carton.

HDPE bottle pack for 28 and 30:

The HDPE bottle is a white, opaque 100 ml HDPE bottle with a white polypropylene, round cylindrical 38 mm cap with a heat seal liner.

HDPE bottle pack for 84 and 90:

The HDPE bottle is a white, opaque 250 ml HDPE bottle with a white polypropylene, round cylindrical 38 mm cap with a heat seal liner.

The cap is a white polypropylene, round cylindrical cap with a heat seal liner and printed with "SEALED for YOUR PROTECTION" in black. The bottle also contains a desiccant.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

SONKE PHARMACEUTICALS (PTY) LTD

Ground Floor, Tugela House

Riverside Office Park

1303 Heuwel Avenue

Centurion

8. REGISTRATION NUMBER:

47/20.2.8/0483

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 June 2014

10. DATE OF REVISION OF THE TEXT

17 October 2022

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