SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RIZENE, 600 mg/200 mg/300 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of **RIZENE** contains:
Efavirenz 600 mg
Emtricitabine 200 mg
Tenofovir disoproxil fumarate 300 mg

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

RIZENE is a pink coloured, capsule shaped, film-coated tablet debossed with “H” on one side and “128” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RIZENE 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

Adults

Take one **RIZENE** film-coated tablet daily on an empty stomach.
Dosing at bedtime may improve the tolerability of nervous system symptoms.

Paediatrics

RIZENE is not recommended for use by patients under the age of 18 years.

Renal impairment

RIZENE is a fixed dose combination and should not be used by patients that require dose adjustment, such as those with moderate or severe renal impairment resulting in a creatinine clearance of less than 50 ml/min.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to efavirenz, emtricitabine, tenofovir disoproxil fumarate or to any of the components listed in section 6.1.
- A history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART).
- Pregnancy and lactation (see section 4.6).
- Patients with moderate to severe renal impairment i.e. creatinine clearance of less than 50 ml/min (see section 4.4 and 5.2).
- **RIZENE** should not be used concurrently with the following medicinal products due to CYP3A4 competition: terfenadine, astemizole, bepridil, cisapride, ergot derivatives, midazolam, pimozide or triazolam. Failure to observe this contraindication can result in reduced metabolism of these medicines and may result in serious and/or life-threatening side effects such as cardiac dysrhythmias, prolonged sedation and/or respiratory depression (see section 4.5).
- **RIZENE** and voriconazole should not be administered concurrently because voriconazole plasma concentrations are reduced significantly by efavirenz (see section 4.5).
- **RIZENE** should not be co-administered 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 sections 4.4 and 4.5).
- Administration to patients with:
  - a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
  - a history of symptomatic cardiac dysrhythmia or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
  - severe disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.
- Co-administration with medicinal products that are known to prolong the QTc interval (proarrhythmic). These medicinal products include: antiarrhythmics of classes IA and III, neuroleptics, antidepressants, certain antibiotics including some from the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungals, certain non-sedating antihistamines (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see sections 4.4 and 4.5).

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 ANTI-RETROVIRALS (SEE SECTION 4.4).

RIZENE IS NOT INDICATED FOR THE TREATMENT OF CHRONIC INFECTION WITH HEPATITIS B VIRUS (HBV). THE SAFETY AND EFFICACY OF **RIZENE** IN PATIENTS CO-INFECTED WITH HBV AND HIV HAS NOT BEEN ESTABLISHED. PATIENTS ON TENOFOVIR AND EMTRICITABINE HAVE DISPLAYED SEVERE EXACERBATIONS OF HEPATITIS B UPON DISCONTINUATION OF TREATMENT. LIVER FUNCTION SHOULD BE MONITORED CLOSELY FOR SEVERAL MONTHS AFTER DISCONTINUATION OF **RIZENE** IN PATIENTS WITH HIV AND HBV CO-INFECTION. CLINICAL AND LABORATORY FOLLOW-UP IS NECESSARY AND IF APPROPRIATE ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis have been reported, including fatal cases, with the use of nucleoside analogues alone or in combination with other anti-retrovirals, with the majority being in women. Obesity and prolonged nucleoside exposure are potential risk factors. Patients with known risk factors for liver disease should only be given nucleoside analogues under cautious observation.

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.
- Lactate 5 – 10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

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

Any patient that 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) should immediately cease **RIZENE** treatment.

Liver disease
Use of **RIZENE** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **RIZENE** 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.

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

Liver failure
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 cell/µl and female gender.

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

Liver enzymes
In patients with a 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. Caution should be exercised and the risk weighed against the benefits of therapy for patients fitting the above profile as well as those with hepatic impairment.

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

Patients with HIV and hepatitis B or C virus co-infection
Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

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 Professional Information for these medicines. Patients co-infected with HIV and HBV who discontinue **RIZENE** should be closely monitored with both clinical and laboratory follow-up after stopping

treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.
Discontinuation of **RIZENE** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Renal impairment (see section 4.3)
Efavirenz is not predominantly excreted by the kidneys while tenofovir disoproxil fumarate and emtricitabine are excreted by the kidneys. Since **RIZENE** is a fixed-dose combination product and the dose of the individual components cannot be altered, patients with creatinine clearance less than 50 ml/min should not receive **RIZENE**.

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

Renal impairment, has been reported in association with the use of tenofovir disoproxil fumarate (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 **RIZENE**. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment. **RIZENE** should be avoided with concurrent or recent use of a nephrotoxic agent.

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

QTc Prolongation
QTc prolongation has been observed with the use of efavirenz (see sections 4.3 and 4.5). For patients at increased risk of Torsade de Pointes or who are receiving medicinal products with a known risk for Torsade de Pointes, the administration of **RIZENE** is contraindicated (see section 4.3).

Psychiatric symptoms
There have been reports of patients treated with efavirenz, which is a component of **RIZENE,** experiencing serious side effects such as severe depression, suicidal ideation, suicide attempts, aggressive behaviour, paranoid reactions and manic reactions.

Although efavirenz was associated with an increase in these psychiatric experiences, there are other associated factors such as a history of injection medicine use, psychiatric history and the use of psychiatric medication. Other adverse events such as death by suicide, psychosis like behaviour and delusions have been reported.
Patients with psychiatric adverse experiences should seek medical evaluation for an assessment on whether their symptoms are related to the use of efavirenz, and thus **RIZENE** (see section 4.8).

Nervous system symptoms
Nervous system symptoms that may be reported during treatment with **RIZENE** are related to efavirenz, which has the potential to cause: dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, hallucinations, euphoria, confusion, agitation, amnesia, stupor, abnormal thinking and depersonalisation.

Nervous system symptoms are more likely to abate after the first 2 to 4 weeks of therapy. It is important to inform patients that they can expect an improvement with continued therapy and that dosing at bedtime may improve the tolerability of nervous system symptoms.

Co-administration of **RIZENE** with alcohol or psychoactive medicines can result in additive central nervous system effects.

Opportunistic infections
Patients receiving **RIZENE** 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 providers experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts need to be done.

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

Triple nucleoside therapy
There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil fumarate as in **RIZENE**, was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen.

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-natal 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. 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 **RIZENE**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated

biochemical markers. Discontinue use of **RIZENE** until diagnosis of pancreatitis is excluded.

Skin rash
Rashes may occur and are usually mild to moderate maculopapular skin eruptions that occur within the first two weeks of initiating efavirenz therapy. In most cases the rash resolves after one month of continuing efavirenz therapy. If treatment is interrupted due to the rash, it may be re-initiated later. The various skin rashes may be treated with antihistamines and/or corticosteroids if indicated. This may result in faster resolution and improved tolerability of the rash.

RIZENE should be discontinued in patients experiencing the following skin rashes: rashes associated with blistering, desquamation, mucosal involvement, or rashes associated with fever.

Bone effects
The effects of when tenofovir disoproxil fumarate associated changes in bone mineral density and biochemical markers on long-term bone health and future fracture risk, are not known.

Osteomalacia associated with the use of tenofovir has been reported associated with proximal renal tubulopathy (see section 4.8).

HIV patients who have a history of pathologic bone fracture or are at risk for osteopenia should be considered for bone monitoring. Supplementation with Vitamin D and calcium may be beneficial. If bone abnormalities are suspected, then appropriate consultation must be sought.

Bone mineral density
Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as contained in **RIZENE**. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia.
RIZENE may cause a reduction in bone mineral density. The effects of tenofovir disoproxil fumarate-associated changes in bone mineral density on long-term bone health and future fracture risk are currently unknown.
Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.
Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis

have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Convulsions
Patients with a history of convulsions must be monitored for possible convulsions when using efavirenz therapy. Please see section 4.5 for anticonvulsants such as phenytoin and phenobarbital, for the precautions and plasma level monitoring that may be required.

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

Immune Reconstitution Inflammatory Syndrome
Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Paediatric use
Tenofovir disoproxil fumarate has not been adequately investigated for use in paediatric patients and therefore **RIZENE** is not recommended for use in patients under the age of 18 years.

Use in the elderly
In general, elderly patients should be treated cautiously, with heightened awareness that this population group tends to experience decreased hepatic, renal or cardiac function and that they usually have concomitant disease or other medicine therapy. There are insufficient studies on the use of efavirenz, emtricitabine and tenofovir by subjects 65 years and older to determine whether they do respond differently than younger subjects.

Co-administration with related medicines
Do not co-administer **RIZENE** with the following related medicines:

- emtricitabine, tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate and efavirenz.
- lamivudine, which is similar to emtricitabine including lamivudine/zidovudine, abacavir sulphate/lamivudine or abacavir sulphate/lamivudine/zidovudine.

Medicine interactions (see section 4.5)
RIZENE is not recommended for use with products containing St. John's wort (*Hypericum perforatum*). Co-administration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz, with St. John's wort is expected to substantially decrease NNRTI concentrations and this may result in suboptimal levels of efavirenz and lead to loss of virologic response and cause possible resistance to efavirenz or to the class of NNRTIs.

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

4.5 Interaction with other medicines and other forms of interaction (see section 4.3 and 4.4)
Efavirenz
Efavirenz is contraindicated for use with medicines that are eliminated predominantly by CYP3A4 hepatic enzymes and that rely on this isoenzyme for clearance (see section 4.3). Altered plasma concentrations may result after co-administration of efavirenz with medicines that are metabolised by isoenzymes 2C9, 2C19, and 3A4 (which are reportedly inhibited by efavirenz) and CYP3A4 (which is reportedly induced by efavirenz). Appropriate dose adjustments may be necessary. Inducers of the CYP3A4 isoenzyme can be expected to increase elimination of efavirenz resulting in lowered plasma concentrations. Medicines regarded as inducers of CYP3A4 include phenobarbital, rifampicin and rifabutin.

Emtricitabine and tenofovir disoproxil fumarate
Medicines such as acyclovir, adefovir, dipivoxil, cidofovir, ganciclovir, valacyclovir and valganciclovir may cause an increase in serum concentrations of emtricitabine and tenofovir. Emtricitabine and tenofovir are primarily eliminated by the kidneys, and therefore have the potential to interact with medicines that reduce renal function or compete for active tubular secretion. Caution should be exercised when **RIZENE** is given with medicines with potential for this interaction since the serum concentrations of each medicine may increase.

Tenofovir increases the plasma concentrations of didanosine. Suppression of CD4 cell counts have been observed in patients on a combination regimen of tenofovir disoproxil fumarate with didanosine at a daily dose of 400 mg. Patients receiving tenofovir disoproxil fumarate and didanosine should be monitored closely for didanosine-associated adverse events. This combination should be undertaken with caution. Didanosine should be discontinued in patients who develop didanosine-associated adverse events (Table 2 in section 4.5 can be consulted for didanosine dosing adjustment recommendations).

Although the mechanism of interaction is not clearly understood, atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations.
The impact of raised tenofovir serum concentrations may involve a higher incidence of tenofovir-related adverse events including renal disorders. **RIZENE** should be discontinued immediately in patients that experience tenofovir-related side effects. Table 2 in section 4.5 can be consulted for atazanavir dosing adjustment recommendations.

Important medicine interactions for **RIZENE** are summarised in this leaflet and further tabulated in Table 1, based upon investigations of interaction profiles for the individual active ingredients efavirenz, emtricitabine and tenofovir disoproxil fumarate. Please also see section 4.3.
Interaction studies for **RIZENE** have not been conducted and therefore the information herein is not all inclusive but highlights potentially significant interactions.

Table 1: Contraindicated medicines or medicines not recommended for use with RIZENE

Medicine name	**Clinical comment**
Antifungal: Voriconazole	Co-administration is **contraindicated** as efavirenz decreases voriconazole plasma concentrations and therapeutic **efficacy**, whereas voriconazole increases efavirenz plasma concentrations and thereby increasing the risk of efavirenz-related side effects.
Antihistamine: Astemizole	Contraindicated as life-threatening adverse events like cardiac dysrhythmias may occur.
Ergot derivatives: Dihydroergotamine Ergonovine Ergotamine Methylergonovine	Contraindicated as life-threatening adverse events like acute ergot toxicity characterised by peripheral vasospasm and extreme ischaemia may occur.
Anti-retrovirals: Efavirenz Emtricitabine Tenofovir disoproxil fumarate Lamivudine	Use is not recommended as emtricitabine, tenofovir disoproxil fumarate, emtricitabine-tenofovir disoproxil fumarate and efavirenz are already active ingredients in **RIZENE**. Lamivudine is similar to emtricitabine.
Benzodiazepines: Midazolam Triazolam	Contraindicated as life-threatening adverse events such as prolonged or increased sedation or respiratory depression may occur.
Calcium channel blockers: Bepridil	Contraindicated as life-threatening adverse events like cardiac dysrhythmias may occur.

Gastrointestinal motility agent: Cisapride	Contraindicated as life-threatening adverse events like cardiac dysrhythmias may occur.
Neuroleptic: Pimozide	Contraindicated as life-threatening adverse events like cardiac dysrhythmias may occur.
St. John's wort (*Hypericum parforatum*)	Co-administration is not recommended as efavirenz plasma concentrations may be lowered significantly.

Table 2: Medicines with established interactions and dose recommendations due to known or predicted interactions

Concomitant Medicine Class: Medicine name	**Effect**	**Clinical comment**
Antiretroviral agents:		
Protease inhibitors		
Amprenavir	↓ amprenavir concentration	Efavirenz may decrease serum concentrations of amprenavir.
Fosamprenavir calcium	↓ amprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and **RIZENE** with respect to safety and efficacy have not been established. An additional 100 mg/day (300 mg total of ritonavir) is recommended when **RIZENE** is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when **RIZENE** is administered with fosamprenavir plus ritonavir twice daily.
Atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Atazanavir concentrations are decreased by both Tenofovir disoproxil fumarate and efavirenz. Therefore, co-administration of **RIZENE** and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations.
Indinavir	↓ indinavir concentration	The optimal dose of indinavir when given in combination with efavirenz is not known. Increasing the dose to 1 000 mg/8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
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). **If patient monitoring reveals an increased incidence of tenofovir-related side effects RIZENE should be discontinued.**
Ritonavir	↑ efavirenz and ritonavir concentrations	The combination of ritonavir 500 mg every 12 hours and efavirenz 600 mg once daily, is 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 **RIZENE** is used in combination with ritonavir.
Saquinavir	↓ saquinavir concentration	If co-administered with **RIZENE**, saquinavir should not be used as the sole protease inhibitor.
NRTI's		
Didanosine	↑ didanosine concentration	Didanosine-associated side effects such as pancreatitis and neuropathy may result from higher concentrations of didanosine. **There is insufficient data to guide dose-adjustment in adult patients weighing less than 60 kg but for those over 60 kg the dose of didanosine must be decreased to 250 mg if co-administered with RIZENE. Caution must be exercised if co-administration is desired and patients must be monitored closely for didanosine-related side effects. More information will appear on the didanosine professional information.** When co-administered, efavirenz and didanosine may be taken under fasted conditions or with a light meal (less than 400 kcal, 20 % fat). Co-administration of **RIZENE** and a buffered didanosine formulation should be under fasting conditions.
Anticoagulant:		
Warfarin	↑ or ↓ warfarin concentration	Monitor anti-coagulation levels (INR) as efavirenz has the potential to alter coagulation times.
Anticonvulsants		
Carbamazepine	↓ carbamazepine concentration	Alternative anticonvulsant treatment should be selected as the data is insufficient to guide dosing adjustment.

Phenytoin Phenobarbital	↓ anticonvulsant concentration and ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants		
Sertraline	↓ sertraline concentrations	Clinical responses must guide an increase in the sertraline dose.
Antifungals		
Itraconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration	Consider alternative antifungal treatment because clinical dose recommendations are unknown.
Ketoconazole	↓ ketoconazole concentration	The effects of ketoconazole and **RIZENE** are unknown. Efavirenz may decrease plasma concentrations of ketoconazole.
Anti-infective		
Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	No dose adjustment is needed for **RIZENE** when used with clarithromycin. Azithromycin should be considered as an alternative to clarithromycin. Erythromycin and other macrolides have not been studied.
Antimycobacterials		
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.
Rifampicin	↓ efavirenz concentration	Dosing recommendations for concomitant use of **RIZENE** and rifampicin have not been established. Clinical significance of reduced efavirenz concentration is unknown.
Calcium channel blockers		
Diltiazem Others (e.g. felodipine, nicardipine, nefedipine,	↓ diltiazem concentration ↓ desacetyl diltiazem concentration ↓ N-monodesmethyl diltiazem concentration	Diltiazem dose adjustments should be undertaken in consultation with the diltiazem professional information, **RIZENE** dose need not be adjusted., The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response in consultation with the complete professional information for the calcium channel blocker.

verapamil)	↓ calcium channel blocker concentration	
HMG-CoA reductase inhibitors		
Atorvastatin Pravastatin Simvastatin	↓ atorvastatin, pravastatin and simvastatin concentrations	The concentrations of the HMG-CoA reductase inhibitors are decreased by efavirenz and dose adjustments may be done with reference to the individual product professional information.
Narcotic analgesics		
Methadone	↓ methadone concentrations	Co-administration of efavirenz in HIV-infected individuals with a history of injection medicine use caused a decrease in methadone plasma levels and signs of opiate withdrawal. Close patient monitoring and dose adjustment to increase methadone upon appearance of withdrawal symptoms until alleviation of symptoms is recommended. Concomitant administration with **RIZENE** is contraindicated due to the risk for QTc prolongation (see sections 4.3 and 4.4).
Oral contraceptives		
Ethinyloestradiol	↑ ethinyloestradiol concentration	As the potential interaction with efavirenz with oral contraceptives has not been studied, a reliable barrier contraceptive must be used in addition to oral contraceptives.

Efavirenz assay interference

Interference with cannabinoid tests

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, even though efavirenz does not bind to cannabinoid receptors. More specific confirmatory testing was performed with gas chromatography/ mass spectrometry to reveal and confirm negative results. For more information, please consult the professional information for efavirenz.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age who are using **RIZENE** should avoid falling pregnant and should ensure this by using a barrier method of contraception in combination with other methods of contraception. Pregnancy testing should also be conducted prior to initiating **RIZENE** treatment.

Contraception in males and females
Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives, see section 4.5) while on therapy with **RIZENE**. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of **RIZENE** is recommended.

Pregnancy
RIZENE should not be used during pregnancy.

Administration of efavirenz in the first trimester has the potential to cause harm to the unborn foetus and should the woman become pregnant, she should be educated on the potential harm to the foetus.

Efavirenz has been associated with teratogenicity in animals. Retrospective studies of pregnancies with first-trimester exposure to efavirenz as part of a combination regimen have noted a few cases of neural tube defects, including meningomyelocele.

Breastfeeding
RIZENE should not be taken by breast-feeding women. Mothers should be instructed that they may not breastfeed their infants if they are on RIZENE in order to avoid transmission of HIV to the infant.
Efavirenz, emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz, emtricitabine and tenofovir in newborns/infants. A risk to the infants cannot be excluded.

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

4.7 Effects on ability to drive and use machines
Co-administration of **RIZENE** with alcohol or psychoactive medicines can result in additive central nervous system effects. Patients experiencing central nervous system symptoms such as dizziness, impaired concentration and/or drowsiness should avoid tasks related to operation of machinery and other potentially hazardous tasks.

4.8 Undesirable effects
The Professional Information for efavirenz, emtricitabine and tenofovir disoproxil fumarate in combination with other anti-retroviral medicines, can be referred to for additional information **RIZENE** side effects are summarised in the tables below.

Table 3: Side effects associated with the use of RIZENE active ingredients

System Organ Class	Side effects observed with efavirenz	Side effects observed with emtricitabine and tenofovir	Efavirenz, emtricitabine and Tenofovir in combination: The following side effects have been reported to occur
Infections and infestations			*Frequent:* Sinusitis, upper respiratory tract infections, nasopharyngitis
Blood and lymphatic system disorders		*Frequency unknown:* Neutropenia, anaemia	
Immune system disorders			*Frequent*: Immune reconstitution syndrome
Endocrine disorders		*Frequency unknown:* Sweating, nephrogenic diabetes insipidus	*Frequency unknown:* Cushingoid appearance, accumulation of body fat, dorsocervical fat enlargement (buffalo hump)
Metabolism and nutrition disorders	*Frequency unknown:* Anorexia	*Frequent:* Anorexia, lactic acidosis	
Psychiatric disorders	*Frequent:* Impaired concentration, anxiety, nervousness, euphoria, confusion, somnolence, amnesia, abnormal thinking or dreaming *Frequency unknown:* Aggressive	*Frequent:* Anxiety, headaches *Less frequent:* Abnormal dreams *Frequency unknown:* Depression, insomnia	*Frequent:* Depression, insomnia, abnormal dreams

	behaviour, suicidal thoughts or attempts		
Nervous system disorders	*Frequent:* Headache, dizziness, insomnia *Less frequent:* Hypoaesthesia, convulsions, depersonalisation, paraesthesia, nervousness	*Less frequent:* Paraesthesia, peripheral neuropathy, anxiety, insomnia, dizziness, headache	*Frequent:* Somnolence, headache, dizziness
Ear and labyrinth disorders	*Less frequent:* Tinnitus		
Respiratory, thoracic and mediastinal disorders	*Frequency unknown:* Dyspnoea	*Frequent:* Cough, rhinitis, pneumonia *Less frequent:* Dyspnoea	
Gastrointestinal disorders	*Frequent:* Dyspepsia, abdominal pain, pancreatitis, diarrhoea, nausea, vomiting *Frequency unknown:* Constipation, malabsorption	*Frequent:* Dyspepsia, abdominal pain, diarrhoea, nausea, vomiting, flatulence *Less frequent:* Pancreatitis	*Frequent:* Diarrhoea, nausea, vomiting
Hepato-biliary disorders	*Frequent*: Raised liver enzymes *Frequency unknown*: Hepatic failure	*Less frequent:* Hepatotoxicity *Frequency unknown:* Hepatitis	
Skin and subcutaneous tissue disorders	*Frequent:* Pruritis, skin rash	*Frequent:* Rash event, pruritis	*Frequent:* Rash

	Less frequent: Erythema multiforme, Stevens-Johnson syndrome, photoallergic dermatitis, skin discolouration	*Less frequent:* Hyperpigmentation of soles and/or palms, maculopapular and vesiculobullous rash, urticaria	
Musculoskeletal, connective tissue and bone disorders	*Frequent:* Arthralgia, myalgia *Frequency unknown:* Myopathy	*Frequent:* Back pain, bone density decreased (see section 4.4) *Less frequent:* Myalgia, bone pain, osteomalacia, arthralgia, myopathy	
Renal and urinary disorders		*Frequency unknown:* Nephritis, acute renal failure, renal impairment, Fanconi's syndrome, acute tubular necrosis, polyuria, proximal renal tubulopathy	
Reproductive system and breast disorders		*Frequency unknown*: Breast enlargement	
General disorders and administrative site conditions	*Frequency unknown:* Fatigue	*Frequency unknown:* Fatigue	*Frequent:* Fatigue
Investigations	*Less frequent:* Raised serum cholesterol and triglycerides, raised serum amylases	*Frequency unknown:* Elevations of bilirubin, pancreatic amylase, serum glucose, urine glucose, raised serum amylase, hypophosphataemia, raised liver enzymes	*Frequency unknown:* Laboratory abnormalities related to fasting cholesterol, creatine kinase, serum amylase, alkaline phosphatise, AST, ALT, haemoglobin, hyperglycaemia, haematuria, neutrophils, fasting triglycerides,

			hypertriglyceridemia, hypercholesterolaemia, insulin resistance, hyperlactataemia, hyperlipidaemia

Table 4: Side effects reported from post-marketing surveillance of RIZENE

System Organ Class	Efavirenz	Tenofovir	Emtricitabine
Immune system disorders	Allergic reactions, immuno-allergic liver injury failure	Allergic reactions	No additional events have been identified for inclusion in this section.
Endocrine disorders	Gynaecomastia		
Metabolism and nutrition disorders	Redistribution/ accumulation of body fat (see section 4.4), hypercholesterolaemia, hypertriglyceridemia	Hypophosphataemia, lactic acidosis	
Psychiatric disorders	Aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide		
Nervous system disorders	Abnormal co-ordination, ataxia, convulsions, hypoesthesia, tremor		
Eye disorders	Abnormal vision		
Ear and labyrinth disorders	Tinnitus		
Cardiac disorders	Palpitations		
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Dyspnoea	

Gastrointestinal disorders	Constipation, malabsorption		
Hepato-biliary disorders	Hepatic enzyme increases in hepatic failure, hepatitis	Increased liver enzymes, hepatitis	
Skin and subcutaneous tissue disorders	Flushing, erythema multiforme, nail disorders, photoallergic dermatitis, skin discolouration, Stevens-Johnson syndrome	Rash	
Musculo-skeletal, connective tissue and bone disorders	Myopathy	Myopathy, osteomalacia (both associated with proximal renal tubulopathy)	
Renal and urinary disorders		Renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, polyuria, interstitial nephritis (including acute cases)	
General disorders and administrative site conditions	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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Standard supportive treatment should be applied for patients who have overdosed on **RIZENE**. Treatment is based on evidence of toxicity and monitoring of vital signs as well as observation of the patient's clinical status.

Efavirenz

Accidental intake of > 600 mg of efavirenz has resulted in nervous system symptoms such as involuntary muscle contractions.

Unabsorbed efavirenz may be removed by activated charcoal. Efavirenz is not effectively removed by haemodialysis.

Emtricitabine and tenofovir disoproxil fumarate

There is no data of severe side effects for emtricitabine and tenofovir disoproxil fumarate. The available studies are at the prescribed doses and therefore data is limited.

Emtricitabine and tenofovir may be removed by haemodialysis.

A 3-hour haemodialysis period starting 1,5 hours post-dosing (blood flow rate of 400 ml/min and a dialysate flow rate of 600 ml/min) may be able to remove around 30 % of the emtricitabine dose. It is not known whether emtricitabine can be removed by peritoneal dialysis.

The extraction coefficient of 54 % for tenofovir results in efficient removal. A 4-hour haemodialysis session following a 300 mg single-dosing of tenofovir disoproxil fumarate may be able to remove approximately 10 % of the administered dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 20.2.8 Antiviral agents

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

RIZENE is a fixed dose combination film-coated tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate.

Efavirenz

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

Emtricitabine

Emtricitabine is a synthetic nucleoside cytidine analogue and a nucleoside reverse transcriptase inhibitor (NRTI) that is phosphorylated intracellularly to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into the emerging viral DNA, an event

that results in DNA chain termination. Emtricitabine has a low affinity for mammalian DNA polymerases α, β, and ε and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate
Tenofovir disoproxil fumarate is an acyclic nucleoside phosphate diester analogue of adenosine monophosphate and is a nucleotide reverse transcriptase inhibitor (NRTI). Initial diester hydrolysis is required for conversion of tenofovir disoproxil fumarate to tenofovir and subsequently to tenofovir diphosphate through phosphorylations by cellular enzymes. Tenofovir is converted intracellularly in stages to the diphosphate. The tenofovir diphosphate competitively inhibits HIV-1 RT and incorporation into viral DNA. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and after the incorporation into DNA, by DNA chain termination. Tenofovir diphosphate has a low affinity for mammalian DNA polymerases α and β and mitochondrial DNA polymerase γ.

Antiviral activity
Co-formulation of efavirenz and tenofovir or emtricitabine and tenofovir or emtricitabine and efavirenz exhibits additive to synergistic antiviral effects in cell cultures.

Efavirenz
Efavirenz demonstrates additive antiviral activity against HIV-1 when combined with non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delaviridine 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 is not active against HIV-2.

Emtricitabine
In medicine combinations of emtricitabine with NRTIs, NNRTIs and PIs, additive to synergistic effects have been observed.

Tenofovir disoproxil fumarate
In medicine combinations of tenofovir with NRTIs, NNRTIs and PIs, additive to synergistic effects have been observed.

Resistance
Resistance to efavirenz and the emergence of cross-resistant strains to other NNRTIs has been observed.

Resistance to emtricitabine may occur and the emergence of cross-resistance to other NRTIs may occur.

Resistance to tenofovir may be observed in some strains of HIV, and cross-resistance to other reverse transcriptase inhibitors may occur.

Cross-resistance among the medicines tenofovir, lamivudine, emtricitabine, abacavir,

didanosine, may occur in patients whose virus harbours either M184V/I and/or K65R amino acid substitutions. These amino acid substitutions have been observed in cell culture but are also observed in some HIV-1 isolates from subjects failing treatment by the combination of tenofovir with emtricitabine or lamivudine, and either abacavir or didanosine.

5.2 Pharmacokinetic properties

Efavirenz

Following oral administration, efavirenz is absorbed and peak plasma concentrations are achieved in about 3 to 5 hours. Steady state plasma concentrations following multiple doses are observed after about 6 to 10 days. Efavirenz is highly bound to human plasma proteins especially albumin. Efavirenz is predominantly metabolised by hepatic CYP450 isoenzymes CYP3A4 and CYP2B6. CYP450 enzymes are induced by efavirenz, thereby efavirenz induces its own metabolism. The terminal half-life following multiple doses of efavirenz is 40 to 55 hours while the terminal half-life after a single dose is 52 to 72 hours. 14 to 34 % of a dose is excreted via urinary excretion and 16 to 61 % is excreted as unchanged efavirenz via faecal excretion mechanisms.

Emtricitabine

Following oral administration, emtricitabine is absorbed through the gastrointestinal tract. Peak plasma concentrations are achieved within 1 to 2 hours while the plasma elimination half-life is 10 hours. The mean absolute bioavailability of emtricitabine is 93 %. Emtricitabine is bound minimally to plasma proteins with binding reported to be less than 4 %. It is excreted primarily unchanged in the urine and to a lesser extent in the faeces so it is metabolised to a restricted extent. Haemodialysis is partially capable of removing emtricitabine.

Tenofovir disoproxil fumarate

Following single oral dosing, tenofovir disoproxil fumarate 300 mg is absorbed from the gastrointestinal tract. Peak plasma concentrations are achieved after 1 to 2 hours. Oral bioavailability is approximately 25 % in fasted patients. Tenofovir has a plasma elimination half-life of approximately 17 hours after a single oral dose. Distribution of tenofovir is wide spread predominantly into the kidneys and liver and also into other body tissues. Plasma protein binding is minimal at 1 % and to serum proteins at 7 %. Excretion of tenofovir is predominantly via urinary excretion by both active tubular secretion and glomerular filtration. Haemodialysis is capable of removing tenofovir.

Effects of food on oral absorption

RIZENE has not been evaluated in the presence of food.

Efavirenz

Efavirenz administered with a high fat meal can result in AUC increases up to 28 % and C_{max} increases up to 79 %.

Emtricitabine

Emtricitabine and tenofovir disoproxil fumarate combined administrations with a light meal or a

high fat meal can exhibit tenofovir disoproxil fumarate AUC increases of up to 35 % and tenofovir disoproxil fumarate C_{max} increases of up to 15 %, without any effects on emtricitabine exposure.

Tenofovir disoproxil fumarate
Oral bioavailability of tenofovir disoproxil fumarate can be improved from the average 25 % when it is taken with a high fat meal.

Characteristics of specific patient groups
Paediatric and elderly patients
RIZENE has not been studied in patients less than 18 years old and is therefore not recommended for use in this population group. **RIZENE** has not been fully evaluated for use in elderly patients (older than 65 years of age).

Renal impairment
Efavirenz has not been studied in patients with renal impairment. However less than 1 % of efavirenz is excreted unchanged into the urine. Therefore, the impact of renal impairment on the elimination of efavirenz should be minimal.

The pharmacokinetics of emtricitabine and tenofovir disoproxil fumarate are affected in patients with renal insufficiency. When creatinine clearance is less than 50 ml/min, the $AUC_{0-\infty}$ and C_{max} of emtricitabine and tenofovir disoproxil fumarate is increased for both active ingredients (see sections 4.2, 4.3 and 4.4).

Hepatic impairment
The impact of efavirenz on hepatic impairment has not been studied.

There is no evidence of pharmacokinetic changes in patients with hepatic impairment when compared to healthy patients with normal liver function. Emtricitabine is not significantly metabolised by liver enzymes and therefore the impact of liver impairment should be limited.

Studies of tenofovir in non-HIV infected patients with moderate to severe hepatic impairment did not demonstrate substantial pharmacokinetic changes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Croscarmellose sodium
Hydroxypropyl cellulose
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulphate

Film coating:
Opadry II Pink:

Macrogol/polyethylene glycol (E1521)
Iron oxide black (E172)
Iron oxide red (E172)
Polyvinyl alcohol-part hydrolysed (E1203)
Talc (E553b)
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at or below 25 °C. Keep well closed.

6.5 Nature and contents of the container
RIZENE is packed as 28's, 30's, 60's, 84's, 90's, 120's, 180's and 500's in white opaque, heavy weight high density polyethylene (HDPE) bottles with child-resistant closures and a silica gel desiccant sachet.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special precautions

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
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Erand Gardens
Midrand, 1685
Customer care: 0860 ADCOCK/232625

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adcock ingram