SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

ATROIZA, 600 mg, 200 mg, 300 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Efavirenz 600 mg

Emtricitabine 200 mg

Tenofovir disoproxil fumarate 300 mg (which is equivalent to 245 mg of tenofovir disoproxil)

Contains sugar: Lactose monohydrate 120 mg

For full list of excipients, see section 6.1.

WARNING:

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

BE WARRANTED (SEE SECTION 4.4).

3 PHARMACEUTICAL FORM

Film-coated tablets

Pink coloured, capsule shaped, film-coated tablets debossed with “M171” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ATROIZA is indicated for use alone or in combination with other antiretroviral medicines for the treatment of HIV-1 infection in adults.

4.2 Posology and method of administration

Posology

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

Adults

The recommended dose of ATROIZA is one tablet taken orally once daily.

Dose adjustment

If ATROIZA is co-administered with rifampicin, an additional 200 mg/day (800 mg total) of efavirenz is recommended.

It is important to take ATROIZA on a regular dosing schedule to avoid missing doses.

Patients should be told that if they forget to take ATROIZA they should take the missed dose right away, unless it is less than 12 hours until the next day’s dose. In this case, patients should be told not to take the missed dose and to take their next dose at the usual time.

Special populations

Elderly population

Insufficient numbers of elderly patients have been evaluated in clinical studies of the components of ATROIZA to determine whether they respond differently than younger patients. Caution should be

exercised when prescribing ATROIZA to the elderly, keeping in mind the greater frequency of decreased hepatic or renal function in these patients.

Renal impairment

ATROIZA is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 mL/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet.

Hepatic impairment

The pharmacokinetics of ATROIZA have not been studied in patients with hepatic impairment. Patients with mild-to-moderate liver disease (Child-Pugh Grade A or B) may be treated with the normal recommended dose of ATROIZA. Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz.

ATROIZA is contraindicated in patients with severe hepatic impairment.

Paediatric population

Children and adolescents

ATROIZA is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy.

Method of administration

- It is recommended that ATROIZA be swallowed whole with water.
- It is recommended that ATROIZA be taken on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions.
- In order to improve the tolerability to efavirenz with respect to undesirable effects on the nervous system, bedtime dosing is recommended.
- It is anticipated that tenofovir exposure will be approximately 35 % lower following administration of ATROIZA on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food. In virologically suppressed patients, the clinical relevance of this reduction can be expected to be limited. Further data on the clinical translation of the decrease in pharmacokinetic exposure is awaited.

4.3 Contraindications

- Hypersensitivity to emtricitabine, tenofovir, efavirenz or to any of the excipients in ATROIZA (listed in section 6.1).
- ATROIZA must not be used in patients with severe hepatic impairment.
- ATROIZA must not be administered concurrently with cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine and methylergonovine), because competition for cytochrome P450 CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects (for example, cardiac dysrhythmias, prolonged sedation or respiratory depression) (see sections 4.4 and 4.5).
- Herbal preparations containing St. John's Wort (*Hypericum perforatum*) must not be used while taking ATROIZA due to the risk of decreased plasma concentrations and reduced clinical effects of ATROIZA (see section 4.5).
- Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5). Since ATROIZA is a fixed-dose combination medicine, the dose of efavirenz cannot be altered; therefore, voriconazole and ATROIZA must not be co-administered.
- ATROIZA must not be used in patients with moderate to severe renal impairment (creatine clearance < 50 mL/min) (see sections 4.4 and 4.2).
- ATROIZA must not be used during pregnancy and breastfeeding (see section 4.6).
- ATROIZA must not be used in patients younger than 18 years of age due to lack of safety and efficacy.
- Children weighing less than 40 kg.
- ATROIZA must not be used concomitantly with medicines containing any of the components efavirenz, emtricitabine or tenofovir, or who concomitantly take other cytidine analogues, such as lamivudine and adefovir dipivoxil (see section 4.5). However, if ATROIZA is co-administered with rifampicin, an additional dose of efavirenz is recommended (see section 4.2).
- Co-administration with elbasvir/grazoprevir due to the expected significant decreases in plasma concentrations of elbasvir and grazoprevir. This effect is due to induction of CYP3A4 or P-gp by efavirenz and may result in loss of therapeutic effect of elbasvir/grazoprevir (see section 4.5).
- A history of previous liver injury/failure with efavirenz containing antiretroviral therapy (ART).

- 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 arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
  - Severe disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesemia.
- Co-administration with medicines that are known to prolong the QTc interval (proarrhythmic).

  These medicines include:
  - Antiarrhythmics of classes IA and III.
  - Neuroleptics, antidepressive medicines.
  - Certain antibiotics including some medicines of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal medicines.
  - Certain non-sedating antihistamines (terfenadine, astemizole).
  - Cisapride.
  - Flecainide.
  - Certain antimalarials.
  - Methadone (see section 4.5).

4.4 Special warnings and precautions for use

If ATROIZA is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis.

Where discontinuation of therapy with one of the components of ATROIZA is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate should be used. Please refer to the package inserts for these medicines.

If therapy with ATROIZA is discontinued, consideration should be given to the long half-life of efavirenz and long intracellular half-lives of tenofovir and emtricitabine. Because of interpatient variability in these parameters and concerns regarding development of resistance, current HIV treatment guidelines should be consulted, also taking into consideration the reason for discontinuation.

See section 4.3 regarding concomitant use with other medicines.

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, such as contained in ATROIZA, 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 ATROIZA 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 ATROIZA 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 antiretroviral therapy (ART) is not recommended. Measurement of serum lactate levels is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2mmol/litre) and respond as follows:

- Lactate 2 to 5 mmol/litre: monitor regularly and be alert for clinical symptoms.
- Lactate 5 to 10 mmol/litre without symptoms: monitor closely.
- Lactate 5 to 10 mmol/litre with symptoms: STOP all therapy. Exclude all other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate greater than or equal to 10 mmol/litre: STOP all therapy (80 % mortality in case studies).

Patients with HIV and hepatitis B virus co-infection

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. ATROIZA is not indicated for the treatment of chronic HBV infection and the safety and efficacy of ATROIZA have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of emtricitabine (200 mg) and tenofovir disoproxil fumarate. Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue ATROIZA and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

QTc prolongation

QTc prolongation has been observed with the use of efavirenz (see sections 4.5 and 5.1). For patients at increased risk of Torsade de Pointes or who are receiving medicines with a known risk for Torsade de Pointes, consider alternatives to ATROIZA.

Psychiatric symptoms

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions, psychosis-like behaviour and catatonia. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweighs the benefits (see section 4.8).

Nervous system symptoms

Nervous system symptoms have been reported with efavirenz use (see section 4.8). In addition, there have been reports of psychosis-like reactions, such as delusions and inappropriate behaviour (including aggressive reactions), predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in patients with a previous history of depression.

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies. Dizziness was also seen in clinical studies with emtricitabine and tenofovir disoproxil. Headache has been reported in clinical studies with emtricitabine (see section 4.8).

Nervous system symptoms associated with efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms. Patients should be advised that if they experience these symptoms, they should contact their doctor immediately because discontinuation of ATROIZA may be required.

Co-administration of ATROIZA with alcohol or psychoactive medicines can result in additive central

nervous system effects.

Seizures

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicines primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a medicine interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

Renal impairment

Emtricitabine and tenofovir, two of the active ingredients in ATROIZA are principally eliminated by the kidneys. Dosing interval adjustment of emtricitabine and tenofovir is recommended in all patients with creatinine clearance 30 – 49 mL/min. Since this is not possible with a fixed-dose combination, ATROIZA should not be administered to patients with creatinine clearance < 50 mL/min or patients requiring haemodialysis (see sections 4.2 and 4.3).

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 (see section 4.8). The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic medicines. However, some cases occurred in patients without identifiable risk factors.

ATROIZA should be avoided with concurrent or recent use of nephrotoxic medicines. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic medicines. should be carefully monitored for changes in serum creatinine and phosphorous.

Medicine interactions

ALERT: Find out about medicines that should NOT be taken with ATROIZA (see sections 4.4 and 4.5). Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of ATROIZA 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 adefovir dipivoxil, cidofovir, acyclovir, valaciclovir, ganciclovir and valganciclovir.

As a fixed combination, ATROIZA should not be administered concomitantly with other medicines

containing the same active ingredients, emtricitabine or tenofovir disoproxil. ATROIZA should not be co-administered with medicines containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see section 4.2).

Due to similarities between emtricitabine and lamivudine, ATROIZA should not be co-administered with other medicines containing lamivudine, including lamivudine and zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulphate and lamivudine co-formulation or abacavir sulphate, lamivudine and zidovudine co-formulation.

ATROIZA should not be administered concomitantly with adefovir dipivoxil or with medicines containing tenofovir alafenamide.

Co-administration of ATROIZA and didanosine is not recommended (see section 4.5).

Co-administration of ATROIZA and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended since plasma concentrations of velpatasvir and voxilaprevir are expected to decrease following co-administration with efavirenz leading to reduced therapeutic effect of sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

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

Switching from a Protease Inhibitor (PI)-based antiretroviral regimen:

Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to efavirenz/emtricitabine/tenofovir disoproxil may lead to a reduction of the response to the therapy. These patients should be carefully monitored for rises in viral load and, since the safety profile of efavirenz differs from that of protease inhibitors, for adverse reactions.

Bone effects

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomised controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients. These BMD decreases generally improved after treatment discontinuation.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Overall, in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures.

Bone abnormalities such as osteomalacia, which can manifest as persistent or worsening bone pain, and which can infrequently contribute to fractures may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8).

If bone abnormalities are suspected, then appropriate consultation should be obtained.

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 Antiretroviral 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.

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.

Opportunistic infections

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

The risk of HIV transmission to others

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

Skin reactions

Mild-to-moderate rash has been reported with the individual components of ATROIZA. The rash associated with the efavirenz component usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1 % of patients treated with efavirenz (see section 4.8). The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0,1 %. ATROIZA must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Experience with efavirenz in patients who discontinued other antiretroviral medicines of the NNRTI class is limited. ATROIZA is not recommended for patients who have had a life-threatening cutaneous reaction (e.g. Stevens-Johnson syndrome) while taking an NNRTI.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure *in utero*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial

dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown aetiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Effect of food

The administration of ATROIZA with food may increase efavirenz exposure (see section 5.2) and may lead to an increase in frequency of adverse reactions (see section 4.8). It is recommended that ATROIZA be taken on an empty stomach, preferably at bedtime.

Cholesterol

Monitoring of cholesterol and triglycerides should be considered in patients treated with ATROIZA (see section 4.8).

Liver enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medicines associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with ATROIZA needs to be weighed against the unknown risks of significant liver toxicity (see section 4.8).

There is some evidence that efavirenz is associated with three clinical pathological patterns of medicine induced liver failure in HIV positive patients of which the sub massive necrosis histological pattern seems to be associated with a high morbidity or mortality risk and may present many months after therapy has been initiated or even stopped. Risk factors include younger age, CD+ counts ≥ 350 cells/µl and female gender. Patients on ATROIZA or efavirenz containing antiretroviral therapy (ART) should be regularly monitored for jaundice (including a laboratory bilirubin and liver enzymes) and bleeding tendencies.

ATROIZA 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 ATROIZA in patients with both HIV and hepatitis B virus infection have not been established.

Elderly population

Clinical studies of fixed-dose combinations of emtricitabine and tenofovir, as in ATROIZA, did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or medicine therapy.

Paediatric population

Safety and efficacy in paediatric patients have not been established.

Excipients

ATROIZA contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of Interaction

No interaction studies have been conducted using ATROIZA. As ATROIZA contains efavirenz, emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these medicines individually may occur with ATROIZA. Interaction studies with these medicines have only been performed in adults.

As a fixed combination, ATROIZA should not be administered concomitantly with other medicines containing the components, emtricitabine or tenofovir disoproxil. ATROIZA should not be co-administered with medicines containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see section 4.2).

Due to similarities with emtricitabine, ATROIZA should not be administered concomitantly with other cytidine analogues, such as lamivudine and adefovir dipivoxil (see section 4.3) or medicines containing tenofovir alafenamide.

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 iso-enzymes including CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when

co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicines or food (for example, grapefruit juice) which affect CYP3A4 activity.

Concomitant use

ATROIZA must not be administered concurrently with cisapride, midazolam, triazolam, pimozide, bepridil or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

Co-administration of ATROIZA with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of efavirenz/emtricitabine/tenofovir disoproxil with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and ATROIZA are administered concurrently; clinical response and/or medicine levels should be monitored as appropriate.

Sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir

Co-administration of ATROIZA and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended (see section 4.4 and Table below).

QT Prolonging medicines

ATROIZA is contraindicated with concomitant use of medicines that are known to prolong the QTc interval and could lead to Torsade de Pointes, such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressants, certain antibiotics including some medicines of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungals, certain non-sedating antihistamines (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see section 4.3).

Voriconazole

Co-administration of standard doses of efavirenz and voriconazole is contraindicated due to significant increases in the AUC and C_{max} of efavirenz and significant decreases in the AUC and C_{max} of voriconazole. Since ATROIZA is a fixed-dose combination medicine, the dose of efavirenz cannot be altered; therefore, voriconazole and ATROIZA must not be co-administered (see section 4.3).

Renally eliminated medicines

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of ATROIZA, with medicines that reduce renal function or compete for active tubular secretion (e.g.

cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicines.

Use of ATROIZA should be avoided with concurrent or recent use of a nephrotoxic medicine. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2.

Cannabinoid test interaction

Even though efavirenz does not bind to cannabinoid receptors, false-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV infected subjects receiving efavirenz. Confirmatory testing by a more specific method such as gas chromatography/mass spectrometry is recommended in such cases.

Other interactions

Interactions between the components of ATROIZA and protease inhibitors, antiretroviral medicines other than protease inhibitors and other non-antiretroviral medicines are summarised in the Table below.

Interactions between the individual components of ATROIZA and other medicines

Medicines by therapeutic areas	**Effect (increase is indicated as "↑", decrease as "↓", no change as "↔")**	**Recommendation concerning co-administration with ATROIZA**
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Amprenavir/efavirenz	AUC, C_{max} and C_{min} of amprenavir ~↓ 40 %.	Efavirenz has the potential to decrease serum concentrations of amprenavir, hence co-administration of amprenavir and ATROIZA is not recommended.

Atazanavir/ritonavir/ tenofovir disoproxil fumarate	↓ Atazanavir plasma concentration. Co-administration of atazanavir/ ritonavir with tenofovir resulted in increased exposure to tenofovir. Higher tenofovir plasma concentrations could potentiate tenofovir associated adverse events, including renal disorders.	Insufficient data available to make dosing recommendation for atazanavir/ritonavir when dosed with ATROIZA. Co-administration of atazanavir/ ritonavir and ATROIZA is not recommended.
Atazanavir/ritonavir/ efavirenz	↓ Atazanavir plasma concentration. Co-administration of efavirenz with atazanavir in combination with low-dose ritonavir resulted in substantial decreases in atazanavir exposure due to CYP3A4 induction, necessitating dosage adjustment of atazanavir. Co-administration of	

	efavirenz and atazanavir in combination with ritonavir may lead to increases in efavirenz exposure which may worsen the tolerability profile of efavirenz.	
Darunavir/ritonavir/ efavirenz	Darunavir: AUC, C_{min} and C_{max} ↓ (CYP3A4 induction). Efavirenz: AUC, C_{min} and C_{max} ↑ (CYP3A4 inhibition).	ATROIZA in combination with darunavir/ritonavir 800/100 mg once daily may result in suboptimal darunavir C_{min}. If ATROIZA is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. Darunavir/ritonavir should be used with caution in combination with ATROIZA. See ritonavir row below. Monitoring of renal function may be indicated, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic
Darunavir/ritonavir/ tenofovir disoproxil	Darunavir: AUC and C_{min} ↔. Tenofovir: AUC and C_{min} ↑.	

		medicines.
Fosamprenavir/ritonavir/ efavirenz	No clinically significant pharmacokinetic interaction.	ATROIZA and fosamprenavir/ritonavir can be co-administered without dose adjustment. See ritonavir row below.
Indinavir/efavirenz	↔ Efavirenz plasma concentration. ↓ Indinavir plasma concentration. While the clinical significance of decreased indinavir plasma concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz, a component of ATROIZA and indinavir.	Insufficient data available to make dosing recommendation for indinavir when dosed with ATROIZA.
Indinavir/emtricitabine	↔ Indinavir plasma	

	concentration. ↔ Emtricitabine plasma concentration.	
Indinavir/tenofovir disoproxil fumarate	↔ Indinavir plasma concentration. ↔Tenofovir plasma concentration.	
Lopinavir/ritonavir/ tenofovir disoproxil fumarate	↔ Lopinavir/ ritonavir plasma concentration. ↑ Tenofovir plasma concentration. Higher tenofovir plasma concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	Insufficient data to make dosing recommendation for lopinavir/ ritonavir when dosed with ATROIZA. Co-administration of lopinavir/ ritonavir and ATROIZA not recommended.
Lopinavir/ritonavir/ efavirenz	Co-administration of lopinavir/ ritonavir with efavirenz resulted in substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ ritonavir.	
Ritonavir/efavirenz	↑ Ritonavir plasma concentration. ↑ Efavirenz plasma	Co-administration of ritonavir at doses of 600 mg and ATROIZA is not

	concentration (inhibition of CYP-mediated oxidative metabolism). When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (for e.g. dizziness, nausea, paraesthesia and elevated liver enzymes occurred). Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available.	recommended. Using ATROIZA in a regimen including low-dose ritonavir, the possibility of increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction. Monitoring of liver enzymes is recommended when ATROIZA is used in combination with ritonavir.
Saquinavir/efavirenz	↓ Saquinavir plasma concentration; CYP3A4 induction. ↓ Efavirenz plasma concentration.	Co-administration with saquinavir as the sole protease inhibitor and ATROIZA is not recommended.
Saquinavir/tenofovir disoproxil fumarate	↔ Saquinavir plasma concentration. ↔ Tenofovir plasma	

	concentration. Co-administration of tenofovir disoproxil fumarate with ritonavir boosted saquinavir; no pharmacokinetic interaction.	
Saquinavir/ritonavir/ efavirenz	No data are available on the potential interactions of efavirenz with combination of saquinavir and ritonavir. Co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor; see ritonavir above.	Insufficient data are available to make a dosing recommendation for saquinavir/ ritonavir when dosed with ATROIZA. Co-administration of saquinavir/ ritonavir and ATROIZA is not recommended.
CCR5 antagonist		
Maraviroc/efavirenz	Maraviroc: AUC_{12h} and C_{max} ↓. Efavirenz concentrations not measured, no effect is expected.	Refer to the prescribing information for maraviroc for more information.
Maraviroc/tenofovir disoproxil	Maraviroc: AUC_{12h} and C_{max} ↔.	

	Tenofovir concentrations not measured, no effect is expected.	
Integrase strand transfer inhibitor		
Raltegravir/efavirenz	Raltegravir: AUC, C_{12h} and C_{max} ↓ (UGT1A1 induction).	ATROIZA and raltegravir can be co-administered without dose adjustment.
Raltegravir/tenofovir disoproxil	Raltegravir: AUC, C_{12h} and C_{max} ↑ (mechanism of interaction unknown). Tenofovir: AUC, C_{12h} and C_{max} ↓.	
NRTIs and NNRTIs		
NRTIs/efavirenz	Specific interaction studies are not performed with efavirenz and NRTIs, other than lamivudine, zidovudine and tenofovir disoproxil fumarate. Clinically significant interaction is not expected since NRTIs are metabolised via a different route than	Due to similarities with emtricitabine, ATROIZA should not be administered with other cytidine analogues, such as lamivudine.

	efavirenz and unlikely to compete for the same metabolic enzymes and elimination pathways.	
NNRTIs/efavirenz	Interaction not studied. Potential for pharmacokinetic or pharmacodynamic interactions is unknown.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of ATROIZA and another NNRTI is not recommended.
Didanosine/tenofovir disoproxil fumarate	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40 – 60 % increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse events. Cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and	Co-administration of ATROIZA and didanosine is not recommended.

	didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. Decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virologic failure within several tested combinations.	
Hepatitis C antivirals		
Elbasvir/grazoprevir + efavirenz	Elbasvir: AUC and C_{max} ↓ (CYP3A4 or P-gp induction – effect on elbasvir). Grazoprevir: AUC and C_{max} ↓	Co-administration of ATROIZA with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant

	(CYP3A4 or P-gp induction – effect on grazoprevir). Efavirenz: AUC and C_{max} ↔.	decreases in elbasvir/grazoprevir plasma concentrations caused by CYP3A4 or P-gp induction. Refer to the prescribing information for elbasvir/grazoprevir for more information.
Glecaprevir/pibrentasvir/ efavirenz	Expected: Glecaprevir: ↓ Pibrentasvir: ↓	Concomitant administration of glecaprevir/pibrentasvir with efavirenz, a component of ATROIZA may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Co-administration is not recommended. Refer to the prescribing information for glecaprevir/pibrentasvir for more information.
Ledipasvir/sofosbuvir + efavirenz/emtricitabine/ tenofovir disoproxil	Ledipasvir: AUC, C_{max} and C_{min} ↓. Sofosbuvir: AUC and C_{max} ↔. GS-331007[1]:	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal

	AUC, C_{max} and C_{min} ↔. Efavirenz: AUC, C_{max} and C_{min} ↔. Emtricitabine: AUC, C_{max} and C_{min} ↔. Tenofovir: AUC, C_{max} and C_{min} ↑.	disorders. Renal function should be closely monitored.
Sofosbuvir/velpatasvir + efavirenz/emtricitabine/ tenofovir disoproxil	Sofosbuvir: AUC: ↔ Cmax: ↑. GS-331007[1]: AUC, C_{max} and C_{min} ↔. Velpatasvir : AUC, C_{max} and C_{min} ↓. Efavirenz: AUC, C_{max} and C_{min} ↔. Emtricitabine: AUC, C_{max} and C_{min}	Concomitant administration of ATROIZA and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/ voxilaprevir is expected to decrease plasma concentrations of velpatasvir and voxilaprevir. Co-administration is not recommended.

	↔. Tenofovir: AUC, C_{max} and C_{min} ↑.	
Sofosbuvir/velpatasvir/ voxilaprevir + efavirenz/emtricitabine/ tenofovir disoproxil	Interaction only studied with sofosbuvir/velpatasvir. Expected: Voxilaprevir:↓	
Sofosbuvir + efavirenz/emtricitabine/ tenofovir disoproxil	Sofosbuvir: AUC: ↔ C_{max} ↓. GS-331007[1]: AUC: ↔ C_{max}: ↓ Efavirenz: AUC, C_{max} and C_{min} ↔. Emtricitabine: AUC, C_{max} and C_{min}: ↔. Tenofovir: AUC: ↔ C_{max}: ↑ C_{min}: ↔.	ATROIZA and sofosbuvir can be co-administered without dose adjustment.
Antibiotics		

Clarithromycin/efavirenz	↓ Clarithromycin plasma concentration. ↑ Clarithromycin 14-hydroxymetabolite plasma concentration. ↔ Efavirenz plasma concentration (CYP3A4 induction). Rash developed in 46 % of uninfected volunteers receiving efavirenz and clarithromycin.	Clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with ATROIZA.
Antimycobacterials		
Rifabutin/efavirenz	↓ Rifabutin concentration. ↔ Efavirenz concentration (CYP3A4 induction).	Daily dose of rifabutin should be increased by 50 % when given with ATROIZA. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with ATROIZA.
Rifampicin/efavirenz	↓ Efavirenz plasma concentration (CYP3A4 and CYP2B6 induction).	Additional 200mg/day (800mg total) of efavirenz recommended when rifampicin is co-administered with ATROIZA. No dose
Rifampicin/tenofovir disoproxil fumarate	↔ Rifampicin plasma concentration.	

	↔ Tenofovir plasma concentration.	adjustment of rifampicin is recommended when given with ATROIZA.
Antifungals		
Itraconazole/efavirenz	↓ Itraconazole plasma concentration due to CYP3A4 induction. ↔ Efavirenz plasma concentration.	Dose recommendations cannot be made for the use of ATROIZA in combination with itraconazole. Alternative antifungal treatment should be considered.
Posaconazole/efavirenz	Posaconazole: AUC and C_{max} ↓ (UDP-G induction).	Concomitant use of posaconazole and ATROIZA should be avoided unless the benefit to the patient outweighs the risk.
Voriconazole/efavirenz	↓ Voriconazole plasma concentration. ↑ Efavirenz concentration (competitive inhibition of oxidative metabolism). Co-administration of standard doses of efavirenz and voriconazole is	ATROIZA is a fixed-dose combination medicine, the dose of efavirenz cannot be altered; voriconazole and ATROIZA must not be co-administered.

	contraindicated.	
Antimalarials		
Artemether/lumefantrine/ efavirenz	Artemether: AUC and C_{max} ↓. Dihydroartemisinin (active metabolite): AUC and C_{max} ↓. Lumefantrine: AUC: ↓ C_{max}: ↔. Efavirenz: AUC: ↓ C_{max}: ↔ (CYP3A4 induction).	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when ATROIZA and artemether/lumefantrine tablets are co-administered.
Atovaquone and proguanil hydrochloride/ efavirenz	Atovaquone: AUC and C_{max} ↓. Proguanil: AUC: ↓ C_{max}: ↔.	Concomitant administration of atovaquone/proguanil with ATROIZA should be avoided.
ANTICONVULSANTS		
Carbamazepine/ efavirenz	↓ Carbamazepine plasma concentration due to CYP3A4 induction. ↓ Efavirenz plasma	No dose recommendation can be made for the use of ATROIZA with carbamazepine. Alternative anticonvulsants should be

	concentration due to CYP3A4 and CYP2B6 induction. Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.	considered. Carbamazepine plasma levels should be monitored periodically.
Phenytoin and other anticonvulsants	Interaction not studied with efavirenz, emtricitabine or tenofovir disoproxil fumarate. There is a potential for reduction or increase in the plasma concentrations of phenytoin and other anticonvulsants that are substrates of CYP450 iso-enzymes.	When ATROIZA is co-administered with an anticonvulsant that is substrate of CYP450 iso-enzymes, periodic monitoring of anticonvulsant levels to be conducted.
Valproic acid/efavirenz	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid	ATROIZA and valproic acid can be co-administered without dose adjustment. Patients should be monitored for seizure control.

	pharmacokinetics.	
Vigabatrin/efavirenz Gabapentin/efavirenz	Interaction not studied. Clinically significant interactions are not expected as vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and unlikely to compete for same metabolic enzymes and elimination pathways as efavirenz.	ATROIZA and vigabatrin or gabapentin can be co-administered without dose adjustment.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/efavirenz	↓ Sertraline plasma concentration. ↔ Efavirenz plasma concentration (CYP3A4 induction).	When co-administered with ATROIZA sertraline dose increases should be guided by clinical response.
Paroxetine/efavirenz	↔ Paroxetine plasma concentration. ↔ Efavirenz plasma concentration.	ATROIZA and paroxetine can be co-administered.
Fluoxetine/efavirenz	Interaction not studied. Since fluoxetine shares a	ATROIZA and fluoxetine can be co-administered.

	similar metabolic profile with paroxetine i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine.	
Norepinephrine and dopamine reuptake inhibitor		
Bupropion/efavirenz	Bupropion: AUC and C_{max} ↓. Hydroxybupropion: AUC: ↔ Cmax: ↑ (CYP2B6 induction).	Increases in bupropion dose should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
CARDIOVASCULAR MEDICINES		
Calcium channel blockers		
Diltiazem/efavirenz	↓ Diltiazem plasma concentration. ↑ Efavirenz plasma concentration (CYP3A4 induction). Increase in efavirenz pharmacokinetic parameters are not considered clinically significant.	Dose adjustments of diltiazem when co-administered with ATROIZA should be guided by clinical response.

Verapamil, felodipine, nifedipine and nicardipine	When efavirenz is co-administered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme, there is a potential for reduction in the plasma concentrations of the calcium channel blocker.	Dose adjustments of calcium channel blockers when co-administered with ATROIZA should be guided by clinical response.
LIPID-LOWERING MEDICINES		
HMG Co-A reductase inhibitors		
Atorvastatin/efavirenz	↓ Atorvastatin plasma concentration. ↓ Total active HMG Co-A reductase inhibitors concentration.	Cholesterol levels should be periodically monitored when atorvastatin, pravastatin or simvastatin is co-administered with ATROIZA. Co-administration of efavirenz with these statins did not affect efavirenz pharmacokinetic values, although dose adjustment of the statins may be required.
Pravastatin/efavirenz	↓ Pravastatin plasma concentration.	
Simvastatin/efavirenz	↓ Simvastatin plasma concentration. ↓ Total HMG Co-A reductase inhibitors concentration (CYP3A4 induction).	

Rosuvastatin/efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces, therefore interaction with efavirenz is not expected.	ATROIZA and rosuvastatin can be co-administered without dose adjustment.
HORMONAL CONTRACEPTIVES		
Ethinyl oestradiol/ efavirenz	↑ Ethinyl oestradiol plasma concentration. ↔ Efavirenz plasma concentration. Clinical significance of the effect on ethinyl oestradiol AUC is not known.	Because the potential interaction of efavirenz, a component of ATROIZA, in combination with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.
Ethinyl oestradiol/ tenofovir disoproxil fumarate	↔ Ethinyl oestradiol plasma concentration. ↔ Tenofovir plasma concentration.	
Injection: Depomedroxy progesterone acetate (DMPA)/efavirenz (150 mg IM single dose DMPA)	In a 3-month interaction study, no significant differences in MPA pharmacokinetic parameters were found between subjects receiving	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).

	efavirenz-containing antiretroviral therapy and subjects receiving no antiretroviral therapy.	
Implant: Etonogestrel/efavirenz	Decreased exposure of etonogestrel may be expected (CYP3A4 induction).	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
OPIOIDS		
Methadone/efavirenz	↓ Methadone plasma concentration (CYP3A4 induction). In a study of HIV infected intravenous medicine users, co-administration of efavirenz with methadone 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 receiving methadone and ATROIZA concomitantly should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Methadone/tenofovir	↔ Methadone plasma	

disoproxil fumarate	concentration. ↔ Tenofovir plasma concentration.	
Buprenorphine/naloxone/ efavirenz	Buprenorphine: AUC: ↓. Norbuprenorphine: AUC: ↓. Efavirenz: No clinically significant pharmacokinetic interaction.	Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine may not be necessary when co-administered with ATROIZA.
HERBAL MEDICINES		
St. John's Wort (*Hypericum perforatum*)/ efavirenz	↓ Efavirenz plasma concentration by concomitant use of St. John's Wort due to induction of medicine metabolising enzymes and/or transport proteins by St. John's Wort. This may result in loss of therapeutic effect and development of resistance (see section 4.3).	Co-administration of ATROIZA and St. John's Wort is contraindicated. If a patient is taking St. John's Wort, discontinue use of St. John's Wort and check viral levels and efavirenz levels. Efavirenz levels may increase on discontinuing St. John's Wort. The inducing effect of St. John's Wort may persist for at least 2 weeks after cessation of treatment.

ANTICOAGULANTS		
Warfarin/efavirenz Acenocoumarol/ efavirenz	Plasma concentrations and effects of warfarin or acenocoumarol are potentially increased or decreased by efavirenz.	Dose adjustment of warfarin or acenocoumarol may be required when co-administered with ATROIZA.

[1] The predominant circulating metabolite of sofosbuvir.

Studies conducted with other medicines:

There were no clinically significant pharmacokinetic interactions when efavirenz was administered with azithromycin, cetirizine, fosamprenavir/ritonavir, lorazepam, zidovudine, aluminium/magnesium hydroxide antacids, famotidine or fluconazole. The potential for interactions with efavirenz and other azole antifungals, such as ketoconazole, has not been studied.

There were no clinically significant pharmacokinetic interactions when emtricitabine was administered with stavudine, zidovudine or famciclovir. There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with emtricitabine, or ribavirin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Pregnancy should be avoided in women receiving ATROIZA. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives) while on therapy with ATROIZA. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of ATROIZA is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of ATROIZA.

Pregnancy

ATROIZA is contraindicated in pregnancy and lactation.

There are no adequate or well-controlled studies of ATROIZA or its components in pregnant women.

A small number of cases of neural tube defects, including meningomyelocele, have been reported but causality has not been established. Studies of efavirenz in animals have shown reproductive toxicity including marked teratogenic effects.

Breastfeeding

Studies in rats have demonstrated that efavirenz and tenofovir are excreted in milk; concentrations of efavirenz were much higher than those in maternal plasma. It is not known whether efavirenz, emtricitabine or tenofovir are excreted in human milk. Because of the potential for both HIV transmission and the potential for serious undesirable effects in breastfeeding infants, mothers should be instructed not to breastfeed if they are receiving ATROIZA.

Fertility

No information available.

4.7 Effects on ability to drive and use machines

Efavirenz, and therefore ATROIZA, may cause dizziness, impaired concentration, and/or drowsiness and have a minor effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision. Co-administration of ATROIZA with alcohol or psychoactive medicines can result in additive central nervous system effects.

4.8 Undesirable effects

a. Summary of the safety profile

- Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme, neuropsychiatric adverse reactions (including severe depression, death by suicide, psychosis-like behaviour, seizures), severe hepatic events, pancreatitis and lactic acidosis (sometimes fatal) have been reported.
- Rare events of renal impairment, renal failure and uncommon events of proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have also been reported. Monitoring of renal function is recommended for patients receiving ATROIZA (see section 4.4).
- Discontinuation of ATROIZA therapy in patients co-infected with HIV and HBV may be associated

with severe acute exacerbations of hepatitis (see section 4.4).

- The administration of ATROIZA with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 5.2).

b. Tabulated list of adverse reactions

Adverse reactions associated with the use of ATROIZA

Treatment-emergent adverse reactions considered possibly or probably related to ATROIZA which have not been associated with one of the individual components of ATROIZA include:

Common

- Anorexia.

Uncommon

- Dry mouth.
- Incoherent speech.
- Increased appetite.
- Libido decreased.
- Myalgia.

Adverse reactions associated with ATROIZA listed by the component(s) of ATROIZA to which the adverse reactions are attributable

	ATROIZA		
	Efavirenz	**Emtricitabine**	**Tenofovir disoproxil**
Blood and lymphatic system disorders			
Frequent		Neutropenia	
Less frequent		Anaemia[1]	
Immune system disorders			
Frequent		Immuno-allergic reaction (liver injury/failure)	

Less frequent	Hypersensitivity		
Metabolism and nutrition disorders			
Frequent	Hypertriglyceridaemia[3]	Hyperglycaemia, hypertriglyceridaemia	Hypophosphataemia[2]
Less frequent	Hypercholesterolaemia[3]		Hypokalaemia[2], lactic acidosis
Psychiatric disorders			
Frequent	Depression (severe in 1,6 %)[3], anxiety[3], abnormal dreams[3], insomnia[3]	Abnormal dreams, insomnia	
Less frequent	Suicide attempt[3], suicide ideation[3], psychosis[3], mania[3], paranoia[3], hallucination[3], euphoric mood[3], affect lability[3], confusional state[3], aggression[3], catatonia[3] completed suicide[3,4], delusion[3,4], neurosis[3,4]		
Nervous system disorders			
Frequent	Cerebellar coordination and balance disturbances[3], somnolence (2,0 %)[3],	Headache, dizziness	Dizziness, headache

	headache (5,7 %)[3], disturbance in attention (3,6 %)[3], dizziness (8,5 %)[3]		
Less frequent	Convulsions[3], amnesia[3], thinking abnormal[3], ataxia[3], coordination abnormal[3], agitation[3], tremor		
Eye disorders			
Less frequent	Vision blurred		
Ear and labyrinth disorders			
Less frequent	Tinnitus, vertigo		
Vascular disorders			
Less frequent	Flushing		
Gastrointestinal disorders			
Frequent	Diarrhoea, vomiting, abdominal pain, nausea	Diarrhoea, nausea, elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
Less	Pancreatitis		Pancreatitis

frequent			
Hepatobiliary disorders			
Frequent	Elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated gamma-glutamyltransferase (GGT)	Elevated serum AST and/or elevated serum ALT, hyperbilirubinaemia	Increased transaminases
Less frequent	Hepatitis acute, hepatic failure[3,4]		Hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders			
Frequent	Rash (moderate-severe[3]), pruritus	Vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)[1]	Rash
Less frequent	Stevens-Johnson syndrome, erythema multiforme[3], severe rash, photoallergic dermatitis	Angioedema[4]	Angioedema
Musculoskeletal and connective tissue disorders			
Frequent		Elevated creatine	Decreased bone

		kinase	mineral density, rhabdomyolysis[2], muscular weakness[2]
Less frequent			Osteomalacia (manifested as bone pain and infrequently contributing to fractures)[2,4], myopathy[2]
Renal and urinary disorders			
Less frequent			Increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome, renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis)[4], nephrogenic diabetes insipidus
Reproductive system and breast disorders			
Less frequent	Gynaecomastia		
General disorders and administration site conditions			
Frequent	Fatigue	Pain, asthenia	Asthenia

[1] Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.

[2] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[3] See section 4.8 – Description of selected adverse reactions for more details.

[4] This adverse reaction was identified through post-marketing surveillance for either efavirenz, emtricitabine or tenofovir disoproxil.

c. Description of selected adverse reactions

Laboratory abnormalities

Raised liver enzyme values have occurred, particularly in patients with viral hepatitis. Raised serum cholesterol and triglyceride concentrations have been reported.

Liver enzymes

Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in patients treated with 600 mg of efavirenz.

Elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity (see section 4.4).

Lipids

Increases in total cholesterol of 10 to 20 % have been observed in some uninfected volunteers receiving efavirenz. Increases in non-fasting total cholesterol and HDL of approximately 20 % and 25 %, respectively, were observed in patients treated with efavirenz + ZDV + STC and of approximately 40 % and 35 % in patients treated with efavirenz + IDV. The effects of efavirenz on triglycerides and LDL were not well characterised. The clinical significance of these findings is unknown (see section 4.4).

Rash

Rashes were usually mild-to-moderate maculopapular skin eruptions that occurred within the first two weeks of initiating therapy with efavirenz. In most patients, rash resolved with continuing therapy with efavirenz within one month. ATROIZA can be reinitiated in patients interrupting therapy because of rash.

Use of appropriate antihistamines and/or corticosteroids is recommended when ATROIZA is

restarted.

Psychiatric symptoms

Patients with a history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions listed in the efavirenz column (see section 4.8 b. Tabulated list of adverse reactions).

Nervous system symptoms

Nervous system symptoms are common with efavirenz, one of the components of ATROIZA. They usually begin during the first one or two days of efavirenz therapy and generally resolve after the first two to four weeks. They may occur more frequently when ATROIZA is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms (see section 4.2).

Hepatic failure with efavirenz

Hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, as reported post-marketing, were sometimes characterised by a fulminant course, progressing in some cases to transplantation or death.

Renal impairment

As ATROIZA may cause renal damage, monitoring of renal function is recommended (see sections 4.4 and 4.8 a. Summary of the safety profile). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medicines) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

Lactic acidosis

Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as severe hepatic impairment (CPT, Class C) (see section 4.3), or patients receiving concomitant medicines known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of cART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to cART. The frequency of this is unknown (see section 4.4).

d. Paediatric population

Insufficient safety data are available for children below 18 years of age. ATROIZA is not recommended in this population (see section 4.2).

e. Other special populations

Elderly population

ATROIZA has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased hepatic or renal function, therefore caution should be exercised when treating elderly patients with ATROIZA (see section 4.2).

Patients with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any patient with mild renal impairment treated with ATROIZA (see sections 4.2, 4.4 and 5.2).

HIV/HBV or HCV co-infected patients

The adverse reaction profile of efavirenz, emtricitabine and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis may occur

after discontinuation of treatment (see section 4.4).

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Emtricitabine

Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine (200 mg).

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

Tenofovir disoproxil fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir 300 mg is available. The effects of higher doses are not known.

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

Efavirenz

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms and involuntary muscle contractions. Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed medicine. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the medicine from the blood.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antiviral agents

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

Mechanism of action

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Efavirenz non-competitively inhibits HIV-1 reverse transcriptase (RT) and does not significantly inhibit human immunodeficiency virus-2 (HIV-2) RT or cellular deoxyribonucleic acid (DNA) polymerases (α, β, γ, and δ). Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

Emtricitabine and tenofovir are nucleoside reverse transcriptase inhibitors (NRTIs) and are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. *In vitro* studies have shown that both emtricitabine and tenofovir can be phosphorylated when combined in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases.

Cardiac electrophysiology

The effect of efavirenz on the QTc interval was evaluated. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90 % confidence interval are 8,7 ms and 11,3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see section 4.5).

Antiviral activity in vitro

In combination studies evaluating the *in vitro* antiviral activity of efavirenz and emtricitabine together, efavirenz and tenofovir together, and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.

Resistance

Resistance to efavirenz can be selected *in vitro* and resulted in single or multiple amino acid substitutions in HIV-1 RT. K103N was the most frequently observed RT substitution in viral isolates from patients who experienced rebound in viral load during clinical studies of efavirenz. Cross-resistance profiles for efavirenz, nevirapine and delavirdine *in vitro* demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs.

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

enzyme targets involved.

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

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

Resistance analysis was performed on plasma HIV-1 isolates from patients with confirmed HIV RNA > 400 copies/mL at week 144 or early study medicine discontinuation where efavirenz, emtricitabine and tenofovir disoproxil fumarate were used as individual formulations in antiretroviral treatment-naïve patients.

Genotypic resistance to efavirenz, predominantly the K103N mutation, occurred most frequently.

The M184V/I mutation was observed in patient isolates in the ATROIZA fumarate group and in patient isolates in the group that received efavirenz and a fixed combination of lamivudine and zidovudine.

No patient in either treatment group developed the K65R mutation and no patient in the ATROIZA fumarate group developed novel mutations associated with phenotypic resistance to either

5.2 Pharmacokinetic properties

Adults

Emtricitabine

Absorption

Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 – 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,022 – 200 µg/mL. Median (range) fasted oral bioavailability of emtricitabine is 92 % (83,1 – 106,4 %). Mean (± SD) C_{max} (maximum plasma concentrations) of emtricitabine at steady state is 1,8 % ± 0,72 µg/mL and mean (± SD) AUC at steady state is 10,0 ± 3,12 µg.hr/mL.

Distribution

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.

Elimination

Emtricitabine is eliminated by a combination of glomerular filtration and active secretion with a renal clearance in adults with normal renal function of 213 ± 89 mL/min (mean ± SD). Following a single oral dose of emtricitabine (200 mg), the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate

Absorption

Following oral administration of a single 300 mg dose of tenofovir DF to HIV-infected patients in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1,0 ± 0,4 hours, mean (± SD) C_{max} and AUC values were 296 ± 90 ng/mL and 2,287 ± 685 ng.hr/mL, respectively.

Biotransformation

Median (range) fasted oral bioavailability of tenofovir is 25 % (NC – 45 %). *In vitro* binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01 – 25 µg/mL.

Elimination

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 of tenofovir, the terminal elimination half-life is approximately 17 hours.

Efavirenz

Absorption

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

Distribution

Efavirenz is highly bound (approximately 99,5 – 99,75 %) to human plasma proteins, predominantly albumin.

Elimination

Following administration of ^{14}C-labelled efavirenz, approximately 14 – 34 % of a radio-labelled dose of efavirenz was recovered in the urine (mostly as metabolites) and 16 – 61 % was recovered in faeces (mostly as parent medicine). *In vitro* studies suggest CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce P450 enzymes, resulting in the 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.

Effect of food

The fixed-dose combination ATROIZA has not been evaluated in the presence of food.

Administration of efavirenz capsules with a high fat meal increased the mean AUC and C_{max} of efavirenz by 28 % and 79 %, respectively, compared to administration in a fasted state. Compared to fasted administration, dosing of tenofovir disoproxil fumarate and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35 % and 15 %, respectively without affecting emtricitabine exposures.

ATROIZA is recommended for administration on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 4.8). It is anticipated that tenofovir exposure (AUC) will be approximately 30 % lower following administration of

efavirenz/emtricitabine/tenofovir disoproxil on an empty stomach as compared to the individual component tenofovir disoproxil when taken with food (see section 5.1).

Special populations

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 impart of renal impairment on efavirenz elimination should be minimal.

Emtricitabine and tenofovir disoproxil fumarate

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment. In patients with creatinine clearance < 50 mL/min, C_{max} and $AUC_{0-\alpha}$ of emtricitabine and tenofovir were increased.

Patients with impaired hepatic impairment

Efavirenz

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment.

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 minimal.

Tenofovir disoproxil fumarate

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate 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.

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 weighs less than 13 kg. Emtricitabine has been studied in paediatric patients from 3 months to 17 years of age. ATROIZA is not recommended for paediatric administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir have not been fully evaluated in the elderly (more than 65 years).

Gender

The pharmacokinetics of emtricitabine and tenofovir are similar in male and female patients. Limited data suggest that females may have higher exposure to efavirenz but they do not appear to be less tolerant of efavirenz.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulfate

Tablet coating

Black iron oxide

Polyethylene glycol

Polyvinyl alcohol

Red iron oxide

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original container.

Do not remove from the carton until required for use.

Keep the bottle tightly closed.

6.5 Nature and contents of container

ATROIZA is packed in high density polypropylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene (PP) screw closure with desiccant, packed in an outer carton in 28s and 30s.

ATROIZA is packed in high density polypropylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene (PP) screw closure with desiccant without outer carton in pack sizes of 28s and 30s.

ATROIZA is packed in high density polypropylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene (PP) screw closure along with wad containing aluminium induction sealing liner with desiccant sieve sachet, packed in an outer carton in 90s.

ATROIZA is packed in high density polypropylene (HDPE) bottle pack comprising of blue opaque wide mouth HDPE bottle with a blue opaque polypropylene screw closure with desiccant, packed in an outer carton in 28s and 30s.

ATROIZA is packed in high density polypropylene (HDPE) bottle pack comprising of blue opaque wide mouth HDPE bottle with a blue opaque polypropylene screw closure with desiccant sachet or desiccant canister without outer carton, packed in 28s and 30s.

ATROIZA is packed in low density polypropylene (LDPE) bag tied close along with a sieve or canister desiccant in 70s.

ATROIZA is packed in high density polypropylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene screw closure along with wad containing aluminium induction sealing liner with desiccant sieve sachet packed without carton, packed in 84s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

8 REGISTRATION NUMBER

45/20.2.8/0172

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 June 2012

10 DATE OF REVISION OF THE TEXT

To be confirmed