PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CITENVIR 600/200/300 (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg.

Contains titanium dioxide. **CITENVIR** is sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CITENVIR tablets are white to off white, oval shaped, biconvex, film-coated tablets debossed with ‘I48’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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

Special populations

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

Paediatric population

Paediatrics: CITENVIR is not recommended for use in patients less than 18 years of age.

Method of administration

Oral administration.

4.3 Contraindications

CITENVIR is contraindicated in patients with previously demonstrated hypersensitivity to the active substances efavirenz, emtricitabine or tenofovir disoproxil fumarate or any of the excipients of the product (see section 6.1).

A history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART) such as **CITENVIR**.

Severe hepatic impairment (CPT, Class C) (see section 4.4).

CITENVIR should not be administered concurrently with terfenadine astemizole, bepridil, cisapride, midazolam, pimozide, triazolam or ergot derivatives (for example, ergotamine, dihydroergotamine, ergonovine and methylergonovine) because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g. cardiac dysrhythmias, prolonged sedation or respiratory depression) (see section 4.5).

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).

CITENVIR should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see section 4.5).

CITENVIR is contraindicated in patients with moderate to severe renal impairment (creatinine clearance less than 50 mL/min (see section 4.4 and section 5.2).

Co-administration with herbal preparations containing St. John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

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 dysrhythmias 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 (prodysrhythmic). These medicines include:

- antidysrhythmics of classes IA and III,
- neuroleptics, antidepressive medicines,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- flecainide,
- certain antimalarials,
- methadone (see sections 4.4 and 4.5).

Pregnancy and lactation.

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 ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (see section 4.4).

CITENVIR IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF **CITENVIR** HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE OR TENOFOVIR, WHICH ARE COMPONENTS OF **CITENVIR**. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY

WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE CO-INFECTED WITH HIV AND HBV AND DISCONTINUE **CITENVIR**. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

Lactic acidosis/hyperlactataemia/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with **CITENVIR** 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).

Use of **CITENVIR** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

Routine testing of serum lactate levels in asymptomatic patients on ART such as **CITENVIR** is not recommended. Measurement of serum lactate levels is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis.

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

Lactate 2 to 5 mmol/L with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.

Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate: STOP NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism).

Lactate greater than 10 mmol/L: STOP all therapy (80 % mortality).

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

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

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

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or post-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 (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs and symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving **CITENVIR**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **CITENVIR** until diagnosis of pancreatitis is excluded.

Liver disease

Use of **CITENVIR** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **CITENVIR** has not been established in patients with significant underlying liver disorders/diseases.

CITENVIR is contraindicated in patients with severe hepatic impairment (see section 4.3) and not recommended in patients with moderate hepatic impairment. Since efavirenz is principally metabolised by the CYP system, caution should be exercised in administering **CITENVIR** to patients with mild hepatic impairment. These patients should be carefully monitored for efavirenz adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals.

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 or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with **CITENVIR** needs to be weighed against the potential risks of significant liver toxicity. In such patients, temporary or permanent discontinuation of treatment must be considered (see section 4.8).

In patients treated with other medicinal products associated with liver toxicity, monitoring of liver enzymes is also recommended.

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 relevant professional information for these medicines.

It is recommended that all patients with HIV be tested for the presence of chronic HBV before initiating antiretroviral therapy. **CITENVIR** is not indicated for the treatment of chronic HBV infection and the safety and efficacy of **CITENVIR** have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued emtricitabine or tenofovir DF. In some of these patients treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients co-infected with HIV and HBV who discontinue **CITENVIR** should be closely monitored for both clinical and laboratory follow-up for at least 4 months after stopping treatment. If appropriate, re-initiation of anti-hepatitis B therapy may be warranted.

In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

QTc Prolongation

QTc prolongation has been observed with the use of efavirenz (see section 4.5). 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 **CITENVIR**.

Co-administration with related medicines

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

CITENVIR should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.

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

Co-administration of **CITENVIR** 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).

No data are available on the safety and efficacy of **CITENVIR** in combination with other antiretroviral agents.

Switching from protease inhibitor (PI) based antiretroviral regimen

Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to **CITENVIR** 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.

Medicine interactions (see section 4.5)

Concomitant use of **CITENVIR** and St. John's wort (*hypericum perforatum*) or St. John's wort-containing products is contraindicated. Co-administration of NNRTIs, including efavirenz, with St. John's wort is expected to

substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

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

Psychiatric symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. These include severe depression, suicidal ideation and attempt, aggressive behaviour and psychotic reactions including paranoia and mania.

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 with serious psychiatric adverse experiences, such as severe depression, psychosis or suicidal ideation, should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see section 4.4, Efavirenz below).

Nervous system symptoms

Symptoms include agitation, amnesia, confusion, dizziness, euphoria, headache, insomnia, somnolence, impaired concentration, stupor, abnormal thinking or dreaming.

These events usually begin within the first 1 or 2 days of treatment and generally resolve within the first 2 to 4 weeks.

Patients should be informed that these frequent symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of the less frequent psychiatric symptoms (see section 4.4, Psychiatric symptoms).

Dosing at bedtime may improve the tolerability of these nervous system symptoms (see section 4.2).

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

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 medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug 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 (see section 4.3)

Emtricitabine and tenofovir are principally eliminated by the kidney, however efavirenz is not.

Since **CITENVIR** is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance less than 50 mL/min should not receive **CITENVIR**.

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

Renal impairment, renal failure, elevated creatinine, including cases of acute renal failure and Fanconi's syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir DF (see section 4.4, Tenofovir below).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy with **CITENVIR** and renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients with a history of renal dysfunction or in patients who are at risk of renal dysfunction, a more frequent monitoring of renal function is required.

If serum phosphate is < 1.5 mg/dl (0.48 mmol/L) or creatinine clearance is decreased to < 50 mL/min in any patient receiving **CITENVIR**, renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since **CITENVIR** is a combination product and the dosing interval of the individual components cannot be altered, treatment with **CITENVIR** must be interrupted in patients with confirmed creatinine clearance < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/L). Interrupting treatment with **CITENVIR** should also

be considered in case of progressive decline of renal function when no other cause has been identified. Where discontinuation of therapy with one of the components of **CITENVIR** is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil are available.

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

If concomitant use of **CITENVIR** and nephrotoxic medicines (e.g. aminoglycosides, amphotericin B, forcarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2) is unavoidable, renal function must be monitored weekly (see section 4.5)

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

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of **CITENVIR** is increased due to decreased clearance. **CITENVIR** is contraindicated in patients with moderate to severe renal impairment (creatinine clearance less than 50 mL/min.

Liver Enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended (see section 4.4, Patients Co-infected with HIV and HBV). In patients with persistent elevations of serum transaminases to > 5 X the upper limit of the normal range, the benefit of continued therapy with **CITENVIR** needs to be weighed against the unknown risks of significant liver toxicity (see section 4.8).

Because of the extensive cytochrome P450 mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering **CITENVIR** to these patients (see section 4.3).

Weight and metabolic parameters

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

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.

Patients with HIV-1 harbouring mutations

CITENVIR should be avoided in patients with HIV-1 harbouring the K65R, M184V/I or K103N mutation.

Reproductive Risk Potential

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving **CITENVIR** (see section 4.3). Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of **CITENVIR**.

Paediatric population

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

Use in the elderly

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

EFAVIRENZ

Efavirenz is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C), and should be used with caution, and liver enzymes values monitored, in patients with mild to moderate liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution should be exercised in patients with a history of seizures or psychiatric disorders, including depression.

Mild to moderate rash has been reported with the individual components of **CITENVIR**. 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. Efavirenz should be stopped if a severe skin rash, associated with blistering, desquamation, mucosal involvement, or fever develops. Experience with efavirenz in patients who discontinued other antiretroviral medicines of the NNRTI class is limited. **CITENVIR** is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking an NNRTI.

Monitoring of serum lipids and blood-glucose may be considered during efavirenz treatment.

Food may increase exposure to efavirenz and lead to an increase in the frequency of undesirable effects (see section 4.8). It is recommended that **CITENVIR** be taken on an empty stomach, preferably at bedtime.

False-positive results in some urinary cannabinoid tests have been reported in subjects receiving efavirenz.

There is some evidence that efavirenz such as contained in **CITENVIR** is associated with three clinical pathological patterns of drug induced liver failure in HIV positive patients of which the sub massive necrosis histological pattern seems to be associated with a high morbidity/mortality risk and may present many months after therapy has been initiated or even stopped. Risk factors include younger age, CD4+ counts $\geq$ 350 cells/mm^3 and female gender.

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

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

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

EMTRICITABINE

Treatment with emtricitabine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology.

Emtricitabine should be given with caution to patients with hepatomegaly or other risk factors for liver disease.

Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events; treatment should be interrupted or stopped if there is evidence of exacerbation of liver disease. It is recommended that all patients should be tested for the presence of hepatitis B infection before treatment is begun. Acute and sometimes severe exacerbations of hepatitis have been reported in hepatitis B-infected patients after stopping treatment with emtricitabine; patients co-infected with HIV and hepatitis B should be closely monitored for several months after stopping treatment.

Emtricitabine should be used with caution and doses adjusted in patients with renal impairment.

TENOFOVIR

Treatment with tenofovir disoproxil fumarate should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. It should be given with caution to patients with hepatomegaly or other risk factors for liver disease. In particular, extreme caution should be exercised in patients with co-existing hepatitis C infection who are receiving interferon alfa and ribavirin. In patients co-infected with hepatitis B, there is a risk of severe acute exacerbation of hepatitis when tenofovir is stopped, and liver function should be monitored closely in such patients for at least several months.

Renal function and serum phosphates should be monitored before treatment is started, every 4 weeks during the first year of therapy, and then every 3 months; in patients with a history of renal impairment or who are particularly at risk, more frequent monitoring may be needed.

Tenofovir should be used with caution, and doses modified in patients with renal impairment. If serum-phosphate concentrations fall markedly or if creatinine clearance is below 50 mL/minute, renal function should be evaluated

within a week, and the dose interval may need to be adjusted or treatment interrupted. Tenofovir disoproxil fumarate may be associated with reduction in bone density and patients should be monitored for evidence of bone abnormalities; bone monitoring should be considered for patients with a history of bone fractures or those at risk of osteopenia.

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 **CITENVIR**, was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen.

Opportunistic infections

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

4.5 Interactions with other medicines and other forms of interactions

(See section 4.3 and section 4.4.)

As **CITENVIR** contains efavirenz, emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with **CITENVIR**.

As a fixed combination, **CITENVIR** should not be administered concomitantly with other medicinal products containing efavirenz, emtricitabine or tenofovir disoproxil. Due to similarities with emtricitabine, **CITENVIR** should not be administered concomitantly with other cytidine analogues, such as lamivudine. **CITENVIR** should

not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.

Efavirenz

Efavirenz is metabolised mainly by cytochrome P450 isoenzymes including CYP3A4. Consequently, it may compete with other medicines metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Enzyme inducers may decrease plasma concentrations of efavirenz; efavirenz itself acts as an enzyme inducer and can reduce plasma concentrations of other medicines. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of reported efavirenz plasma concentrations. Co-administration of efavirenz with medicines primarily metabolised by these isoenzymes may result in altered plasma concentrations of the co-administrated medicine.

Therefore, appropriate dose adjustments may be necessary for these medicines.

Efavirenz exposure may be increased when given with medicinal products (for example ritonavir) or food (for example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example Ginkgo biloba extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated (see section 4.3). Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.4).

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

Efavirenz is contraindicated with medicines that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These medicines include antihistamines (astemizole), calcium channel blockers (bepridil), ergot derivatives (dihydroergotamine, ergometrine, ergotamine and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (midazolam and triazolam). St John's wort decreases the concentration of efavirenz: use with the antiretroviral is contraindicated due to the possible loss of its activity and development of resistance.

Antidiabetics: Fatal lactic acidosis has been reported when metformin is given with didanosine, stavudine and tenofovir.

Other important medicine interaction information for **CITENVIR** is summarised in Table 1. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential medicine interactions; no medicine interaction studies have been conducted using **CITENVIR**. The table include potentially significant interactions, but are not all inclusive.

Table 1

Medicines that are contraindicated or not recommended for use with CITENVIR.

Medicine Class: **Medicine Name**	**Clinical Comment**
Antifungal: voriconazole	CONTRAINDICATED because efavirenz significantly decreases voriconazole plasma concentrations and co-administration may decrease the therapeutic efficacy of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects (see section 4.3).
Antihistamine: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias (see section 4.3).
Anti-migraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues (see section 4.3).
Antiretrovirals: efavirenz, emtricitabine, tenofovir DF, lamivudine	Not for use with **CITENVIR** because the active ingredients-emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz are components of **CITENVIR**. Lamivudine is similar to emtricitabine.

Antiretroviral: atazanavir/ritonavir	NOT RECOMMENDED since insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination with **CITENVIR** (see Table 2).
Antiretroviral: didanosine	NOT RECOMMENDED for co-administration with **CITENVIR** (see Table 2).
Antiviral (Hepatitis C): elbasvir/grazoprevir	CONTRAINDICATED because it may lead to loss of virologic response to elbasvir/grazoprevir (see section 4.3)
Antiviral (Hepatitis C): sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/ voxilaprevir	NOT RECOMMENDED for co-administration with **CITENVIR** (see section 4.4 and Table 2)
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression (see section 4.3).
Calcium channel blocker: bepridil	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias (see section 4.3).
GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias (see section 4.3).
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias (see section 4.3).
St. John's wort (*Hypericum perforatum*)	CONTRAINDICATED: Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

QT prolonging medicines: antidysrhythmics of classes IA and III, neuroleptics and antidepressant medicines, certain antibiotics including some medicines of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal medicines, flecainide, certain antimalarials and methadone (see section 4.3).	CONTRAINDICATED with concomitant use of medicines that are known to prolong the QTc interval and could lead to Torsade de Pointes (see section 4.3).
Renally eliminated medicines: cidofovir nephrotoxic medicines – examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).	NOT RECOMMENDED since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of **CITENVIR** with these 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 **CITENVIR** should be avoided with concurrent or recent use of a nephrotoxic medicine.

Other interactions

Interactions between **CITENVIR** or its individual component(s) and other medicinal products are listed in Table 2 below (increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d.", once daily as "q.d." and once every 8 hours as "q8h"). If available, 90 % confidence intervals are shown in parentheses.

Table 2

Interactions between CITENVIR or its individual components and other medicinal products

Medicinal product by therapeutic areas	**Effect on medicine levels Mean percent change in AUC, C_{max}, C_{min} with 90 % confidence intervals if available (mechanism)**	**Recommendation concerning co-administration with CITENVIR (efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil 245 mg)**
ANTI-INFECTIVES		
HIV antivirals		
Protease inhibitors		
Atazanavir/ritonavir/ Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Atazanavir: AUC: ↓ 25 % (↓ 42 to ↓ 3) Cmax: ↓ 28 % (↓ 50 to ↑ 5) Cmin: ↓ 26 % (↓ 46 to ↑ 10) Co-administration of atazanavir/ritonavir with tenofovir resulted in increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders	Co-administration of atazanavir/ritonavir and **CITENVIR** is not recommended.
Atazanavir/ritonavir/ Efavirenz	Atazanavir (pm): AUC: ↔* (↓ 9 % to ↑ 10 %) C_{max}: ↑ 17 %*	Co-administration of atazanavir/ritonavir and **CITENVIR** is not recommended.

(400 mg q.d./100 mg q.d./600 mg q.d., all administered with food) Atazanavir/ritonavir/ Efavirenz (400 mg q.d./200 mg q.d./600 mg q.d., all administered with food)	(↑ 8 to ↑ 27) C_{min}: ↓ 42 %* (↓ 31 to ↓ 51) Atazanavir (pm): AUC: ↔*/** (↓ 10 % to ↑ 26 %) C_{max}: ↔*/** (↓ 5 % to ↑ 26 %) C_{min}: ↑ 12 %*/** (↓ 16 to ↑ 49) (CYP3A4 induction). *When compared to atazanavir 300mg/ ritonavir 100 mg q.d. in the evening without efavirenz. This decrease in atazanavir C_{min} might negatively impact the efficacy of atazanavir. ** based on historical comparison. Co-administration of efavirenz with atazanavir/ritonavir is not recommended	
Atazanavir/ritonavir/ emtricitabine	Interaction not studied.	Co-administration of atazanavir/ritonavir and **CITENVIR** is not recommended.
Darunavir/ritonavir/ efavirenz	Darunavir: AUC: ↓ 13 %	**CITENVIR** in combination with darunavir/ritonavir 800/100mg once daily may

(300 mg b.i.d.*/100 mg b.i.d./600 mg q.d.) *lower than recommended doses; similar findings are expected with recommended doses.	C_{min}: ↓ 31 % C_{max}: ↓ 15 % (CYP3A4 induction) Efavirenz: AUC: ↑ 21 % C_{min}: ↑ 17 % C_{max}: ↑ 15 % (CYP3A4 inhibition)	result in suboptimal darunavir C_{min}. If **CITENVIR** 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 **CITENVIR**. 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 agents.
Darunavir/ritonavir/ tenofovir disoproxil (300 mg b.i.d.*/100 mg b.i.d./245 mg q.d.) *lower than recommended dose	Darunavir: AUC: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	
Darunavir/ritonavir/ emtricitabine	Interaction not studied. Based on the different elimination pathways, no interaction is expected.	
Fosamprenavir/ritonavir/ efavirenz (700 mg b.i.d./100 mg b.i.d./600 mg q.d.)	No clinically significant pharmacokinetic interaction.	**CITENVIR** and fosamprenavir/ritonavir can be co-administered without dose adjustment. See ritonavir row below.
Fosamprenavir/ritonavir/ emtricitabine	Interaction not studied.	
Fosamprenavir/ritonavir/ tenofovir disoproxil	Interaction not studied.	
Indinavir/Efavirenz (800 mg q8h/200 mg q.d.)	Efavirenz: AUC: ↔	Insufficient data are available to make a dosing recommendation for indinavir when dosed with

	C_{max}: ↔ C_{min}: ↔ Indinavir: AUC: ↓ 31 % (↓ 8 to ↓ 47) C_{min}: ↓ 40 % A similar reduction in indinavir exposures was observed when indinavir 1,000 mg q8h was given with efavirenz 600 mg q.d. (CYP3A4 induction) For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	**CITENVIR**. While the clinical significance of decreased indinavir 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 **CITENVIR**, and indinavir.
Indinavir/Emtricitabine (800 mg q8h/200 mg q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔	
Indinavir/Tenofovir disoproxil (800 mg q8h/245 mg q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔	

	C_{max}: ↔	
Lopinavir/ritonavir/ Tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d./245 mg q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32 % (↑ 25 to ↑ 38) C_{max}: ↔ C_{min}: ↑ 51 % (↑ 37 to ↑ 66) Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with **CITENVIR**. Co-administration of lopinavir/ritonavir and **CITENVIR** is not recommended.
Lopinavir/ritonavir soft capsules or oral solution/Efavirenz Lopinavir/ritonavir tablets/Efavirenz (400/100 mg b.i.d./600 mg q.d.) (500/125 mg b.i.d./600 mg q. d.)	Substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ritonavir. When used in combination with efavirenz and two NRTIs, 533/133 mg lopinavir/ritonavir (soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to lopinavir/ ritonavir (soft	

	capsules) 400/100 mg twice daily without efavirenz (historical data). Lopinavir concentrations: ↓ 30-40 % Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz. Dosage adjustment of lopinavir/ritonavir is necessary when given with efavirenz. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	
Lopinavir/ritonavir/ emtricitabine	Interaction not studied.	
Ritonavir/Efavirenz (500 mg b.i.d./600 mg q.d.)	Ritonavir: Morning AUC: ↑ 18 % (↑ 6 to ↑ 33) Evening AUC: ↔ Morning C_{max}: ↑ 24 % (↑ 12 to ↑ 38) Evening C_{max}: ↔ Morning C_{min}: ↑ 42 % (↑ 9 to ↑ 86)	Co-administration of ritonavir at doses of 600 mg and **CITENVIR** is not recommended. When using **CITENVIR** with low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction.

	Evening C_{min}: ↑ 24 % (↑ 3 to ↑ 50) Efavirenz: AUC: ↑ 21 % (↑ 10 to ↑ 34) C_{max}: ↑ 14 % (↑ 4 to ↑ 26) C_{min}: ↑ 25 % (↑ 7 to ↑ 46) (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 example, 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.	
Ritonavir/Emtricitabine	Interaction not studied.	
Ritonavir/Tenofovir disoproxil	Interaction not studied.	
Saquinavir/ritonavir/ efavirenz	Interaction not studied. For co-administration of efavirenz	Insufficient data are available to make a dosing recommendation for saquinavir/ritonavir when

	with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir above.	dosed with **CITENVIR**. Co-administration of saquinavir/ritonavir and **CITENVIR** is not recommended. Use of **CITENVIR** in combination with saquinavir as the sole protease inhibitor is not recommended.
Saquinavir/ritonavir/ tenofovir disoproxil	There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with ritonavir boosted saquinavir.	
Saquinavir/ritonavir/ emtricitabine	Interaction not studied.	
CCR5 antagonist		
Maraviroc/Efavirenz (100 mg b.i.d./600 mg q.d.)	Maraviroc: AUC12h: ↓ 45 % (↓ 38 to ↓ 51) C_{max}: ↓ 51 % (↓ 37 to ↓ 62) Efavirenz concentrations not measured, no effect is expected.	Refer to the Professional Information for the medicinal product containing maraviroc.
Maraviroc/Tenofovir disoproxil (300 mg b.i.d./245 mg q.d.)	Maraviroc: AUC12h: ↔ C_{max}: ↔ Tenofovir concentrations not measured, no effect is expected.	
Maraviroc/Emtricitabine	Interaction not studied.	

Integrase strand transfer inhibitor		
Raltegravir/Efavirenz (400 mg single dose/-)	Raltegravir: AUC: ↓ 36 % C12h: ↓ 21 % C_{max}: ↓ 36 % (UGT1A1 induction)	**CITENVIR** and raltegravir can be co-administered without dose adjustment.
Raltegravir/Tenofovir disoproxil (400 mg b.i.d./-)	Raltegravir: AUC: ↑ 49 % C12h: ↑ 3 % C_{max}: ↑ 64 % (mechanism of interaction unknown) Tenofovir: AUC: ↓ 10 % C12h: ↓ 13 % C_{max}: ↓ 23 %	
Raltegravir/Emtricitabine	Interaction not studied.	
NRTIs and NNRTIs		
NRTIs/Efavirenz	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine and tenofovir disoproxil. Clinically significant interactions have not been found and would not be expected since the NRTIs are metabolised via a different	Due to the similarity between lamivudine and emtricitabine, a component of **CITENVIR**, **CITENVIR** should not be administered concomitantly with lamivudine (see section 4.4).

	route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.	
NNRTIs/Efavirenz	Interaction not studied.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of **CITENVIR** and another NNRTI is not recommended.
Didanosine/Tenofovir disoproxil	Co-administration of tenofovir disoproxil and didanosine results in a 40-60 % increase in systemic exposure to didanosine.	Co-administration of **CITENVIR** and didanosine is not recommended. Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.
Didanosine/Efavirenz	Interaction not studied.	
Didanosine/Emtricitabine	Interaction not studied.	
Hepatitis C antivirals		
Elbasvir/Grazoprevir + Efavirenz	Elbasvir: AUC: ↓ 54 % C_{max}: ↓ 45 %	Co-administration of **CITENVIR** 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 elbasvir) Grazoprevir: AUC: ↓ 83 % C_{max}: ↓ 87 % (CYP3A4 or P-gp induction - effect on grazoprevir) Efavirenz: AUC: ↔ C_{max}: ↔	decreases in elbasvir/grazoprevir plasma concentrations caused by CYP3A4 or P-gp induction. Refer to the Professional Information for elbasvir/grazoprevir for more information.
Glecaprevir/Pibrentasvir/ Efavirenz	*Expected:* Glecaprevir: ↓ Pibrentasvir: ↓	Concomitant administration of glecaprevir/pibrentasvir with efavirenz, a component of **CITENVIR**, may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Coadministration of glecaprevir/pibrentasvir with **CITENVIR** is not recommended. Refer to the Professional Information for glecaprevir/pibrentasvir for more information.
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/ Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓ 34 % (↓ 41 to ↓ 25) C_{max}: ↓ 34 % (↓ 41 to ↑ 25) C_{min}: ↓ 34 % (↓ 43 to ↑ 24) Sofosbuvir: AUC: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

	C_{max}: ↔ GS-331007[1]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 98 % (↑ 77 to ↑ 123) C_{max}: ↑ 79 % (↑ 56 to ↑ 104) C_{min}: ↑ 163 % (↑ 137 to ↑ 197)	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/ Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 38 % (↑ 14 to ↑ 67) GS-331007[1]: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Concomitant administration of **CITENVIR** and sofosbuvir/velpatasvir orsofosbuvir/ velpatasvir/voxilaprevir is expected to decrease plasma concentrations of velpatasvir and voxilaprevir. Co-administration of **CITENVIR** with sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended (see section 4.4).

	Velpatasvir: AUC: ↓ 53 % (↓ 61 to ↓ 43) C_{max}: ↓ 47 % (↓ 57 to ↓ 36) C_{min}: ↓ 57 % (↓ 64 to ↓ 48) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 81 % (↑ 68 to ↑ 94) C_{max}: ↑ 77 % (↑ 53 to ↑ 104) C_{min}: ↑ 121 % (↑ 100 to ↑ 143)	
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/100 mg q.d.) + Efavirenz/ Emtricitabine/Tenofovir disoproxil	Interaction only studied with sofosbuvir/ velpatasvir. *Expected:* Voxilaprevir: ↓	

(600 mg/200 mg/245 mg q.d.)		
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/ Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19 % (↓ 40 to ↑ 10) GS-331007[1]: AUC: ↔ C_{max}: ↓ 23 % (↓ 30 to ↑ 16) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25 % (↑ 8 to ↑ 45) C_{min}: ↔	**CITENVIR** and sofosbuvir can be co-administered without dose adjustment.
Antibiotics		
Clarithromycin/Efavirenz (500 mg b.i.d./400 mg q.d.)	Clarithromycin: AUC: ↓ 39 % (↓ 30 to ↓ 46) C_{max}: ↓ 26 %	The clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered. Other macrolide antibiotics,

	(↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34 % (↑ 18 to ↑ 53) C_{max}: ↑ 49 % (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ C_{max}: ↑ 11 % (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46 % of uninfected volunteers receiving efavirenz and clarithromycin.	such as erythromycin, have not been studied in combination with **CITENVIR**.
Clarithromycin/ Emtricitabine	Interaction not studied.	
Clarithromycin/Tenofovir disoproxil	Interaction not studied.	
Antimycobacterials		
Rifabutin/Efavirenz (300 mg q.d./600 mg q.d.)	Rifabutin: AUC: ↓ 38 % (↓ 28 to ↓ 47) C_{max}: ↓ 32 % (↓ 15 to ↓ 46) C_{min}: ↓ 45 % (↓ 31 to ↓ 56)	The daily dose of rifabutin should be increased by 50 % when given with **CITENVIR**. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with **CITENVIR**. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological

	Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 12 % (↓ 24 to ↑ 1) (CYP3A4 induction)	response should be considered when making the dose adjustment.
Rifabutin/Emtricitabine	Interaction not studied.	
Rifabutin/Tenofovir disoproxil	Interaction not studied.	
Rifampicin/Efavirenz (600 mg q.d./600 mg q.d.)	Efavirenz: AUC: ↓ 26 % (↓ 15 to ↓ 36) C_{max}: ↓ 20 % (↓ 11 to ↓ 28) C_{min}: ↓ 32 % (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)	When **CITENVIR** is taken with rifampicin in patients weighing 50 kg or greater, an additional 200 mg/day (800 mg total) of efavirenz may provide exposure similar to a daily efavirenz dose of 600 mg when taken without rifampicin. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment. No dose adjustment of rifampicin is recommended when given with **CITENVIR**.
Rifampicin/Tenofovir disoproxil (600 mg q.d./245 mg q.d.)	Rifampicin: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Rifampicin/Emtricitabine	Interaction not studied.	
Antifungals		
Itraconazole/Efavirenz	Itraconazole: AUC: ↓ 39 %	Since no dose recommendation can be made for itraconazole when used with **CITENVIR**, an

(200 mg b.i.d./600 mg q.d.)	(↓ 21 to ↓ 53) C_{max}: ↓ 37 % (↓ 20 to ↓ 51) C_{min}: ↓ 44 % (↓ 27 to ↓ 58) (decrease in itraconazole concentrations: CYP3A4 induction) Hydroxyitraconazole: AUC: ↓ 37 % (↓ 14 to ↓ 55) C_{max}: ↓ 35 % (↓ 12 to ↓ 52) C_{min}: ↓ 43 % (↓ 18 to ↓ 60) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	alternative antifungal treatment should be considered.
Itraconazole/ Emtricitabine	Interaction not studied.	
Itraconazole/Tenofovir disoproxil	Interaction not studied.	
Posaconazole/Efavirenz (-/400 mg q.d.)	Posaconazole: AUC: ↓ 50 % C_{max}: ↓ 45 % (UDP-G induction)	Concomitant use of posaconazole and **CITENVIR** should be avoided unless the benefit to the patient outweighs the risk.
Posaconazole/ Emtricitabine	Interaction not studied.	

Posaconazole/Tenofovir disoproxil	Interaction not studied.	
Voriconazole/Efavirenz (200 mg b.i.d./400 mg q.d.)	Voriconazole: AUC: ↓ 77 % C_{max}: ↓ 61 % Efavirenz: AUC: ↑ 44 % C_{max}: ↑ 38 % (competitive inhibition of oxidative metabolism) Co-administration of standard doses of efavirenz and voriconazole is contraindicated (see section 4.3).	Since **CITENVIR** is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and **CITENVIR** must not be co-administered.
Voriconazole/ Emtricitabine	Interaction not studied.	
Voriconazole/Tenofovir disoproxil	Interaction not studied.	
Antimalarials		
Artemether/Lumefantrine/ Efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg q.d.)	Artemether: AUC: ↓ 51 % C_{max}: ↓ 21 % Dihydroartemisinin (active metabolite): AUC: ↓ 46 % C_{max}: ↓ 38 % Lumefantrine:	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when **CITENVIR** and artemether/lumefantrine tablets are co-administered.

	AUC: ↓ 21 % C_{max}: ↔ Efavirenz: AUC: ↓ 17 % C_{max}: ↔ (CYP3A4 induction)	
Artemether/Lumefantrine/ Emtricitabine	Interaction not studied.	
Artemether/Lumefantrine/ Tenofovir disoproxil	Interaction not studied.	
Atovaquone and proguanilhydrochloride/ Efavirenz (250/100 mg single dose/600 mg q.d.)	Atovaquone: AUC: ↓ 75 % (↓ 62 to ↓ 84) C_{max}: ↓ 44 % (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43 % (↓ 7 to ↓ 65) C_{max}: ↔	Concomitant administration of atovaquone/proguanil with **CITENVIR** should be avoided.
Atovaquone and proguanilhydrochloride/ Emtricitabine	Interaction not studied.	
Atovaquone and proguanilhydrochloride/ Tenofovir disoproxil	Interaction not studied.	
Anticonvulsants		
Carbamazepine/Efavirenz (400 mg q.d./600 mg q.d.)	Carbamazepine: AUC: ↓ 27 %	No dose recommendation can be made for the use of **CITENVIR** with carbamazepine. An alternative

	(↓ 20 to ↓ 33) C_{max}: ↓ 20 % (↓ 15 to ↓ 24) C_{min}: ↓ 35 % (↓ 24 to ↓ 44) Efavirenz: AUC: ↓ 36 % (↓ 32 to ↓ 40) C_{max}: ↓ 21 % (↓ 15 to ↓ 26) C_{min}: ↓ 47 % (↓ 41 to ↓ 53) (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction) Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.	anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.
Carbamazepine/ Emtricitabine	Interaction not studied.	
Carbamazepine/Tenofovir disoproxil	Interaction not studied.	
Phenytoin, Phenobarbital, and other anticonvulsants	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil. There is a	When **CITENVIR** is co-administered with an anticonvulsant that is a substrate of CYP isozymes,

that are substrates of CYP isozymes	potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP isozymes with efavirenz.	periodic monitoring of anticonvulsant levels should be conducted.
Valproic acid/Efavirenz (250 mg b.i.d./600 mg q.d.)	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.	**CITENVIR** and valproic acid can be co-administered without dose adjustment. Patients should be monitored for seizure control.
Valproic acid/ Emtricitabine	Interaction not studied.	
Valproic acid/Tenofovir disoproxil	Interaction not studied.	
Vigabatrin/Efavirenz Gabapentin/Efavirenz	Interaction not studied. Clinically significant interactions are not expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and are unlikely to compete for the same metabolic enzymes and	**CITENVIR** and vigabatrin or gabapentin can be co-administered without dose adjustment.

	elimination pathways as efavirenz.	
Vigabatrin/Emtricitabine Gabapentin/Emtricitabine	Interaction not studied.	
Vigabatrin/Tenofovir disoproxil Gabapentin/Tenofovir disoproxil	Interaction not studied.	
ANTICOAGULANTS		
Warfarin/Efavirenz Acenocoumarol/Efavirenz	Interaction not studied. 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 **CITENVIR**.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 mg q.d./600 mg q.d.)	Sertraline: AUC: ↓ 39 % (↓ 27 to ↓ 50) C_{max}: ↓ 29 % (↓ 15 to ↓ 40) C_{min}: ↓ 46 % (↓ 31 to ↓ 58) Efavirenz: AUC: ↔ C_{max}: ↑ 11 % (↑ 6 to ↑ 16) C_{min}: ↔ (CYP3A4 induction)	When co-administered with **CITENVIR**, sertraline dose increases should be guided by clinical response.

Sertraline/Emtricitabine	Interaction not studied.	
Sertraline/Tenofovir disoproxil	Interaction not studied.	
Paroxetine/Efavirenz (20 mg q.d./600 mg q.d.)	Paroxetine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	**CITENVIR** and paroxetine can be co-administered without dose adjustment.
Paroxetine/Emtricitabine	Interaction not studied.	
Paroxetine/Tenofovir disoproxil	Interaction not studied.	
Fluoxetine/Efavirenz	Interaction not studied. Since fluoxetine shares a similar metabolic profile with paroxetine, i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine.	**CITENVIR** and fluoxetine can be co-administered without dose adjustment.
Fluoxetine/Emtricitabine	Interaction not studied.	
Fluoxetine/Tenofovir disoproxil	Interaction not studied.	
Norepinephrine and dopamine reuptake inhibitor		
Bupropion/Efavirenz	Bupropion: AUC: ↓ 55 %	Increases in bupropion dosage should be guided by clinical response, but the maximum recommended

[150 mg single dose (sustained release)/ 600 mg q.d.]	(↓ 48 to ↓ 62) C_{max}: ↓ 34 % (↓ 21 to ↓ 47) Hydroxybupropion: AUC: ↔ C_{max}: ↑ 50 % (↑ 20 to ↑ 80) (CYP2B6 induction)	dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
Bupropion/Emtricitabine	Interaction not studied.	
Bupropion/Tenofovir disoproxil	Interaction not studied.	
CARDIOVASCULAR AGENTS		
Calcium Channel Blockers		
Diltiazem/Efavirenz (240 mg q.d./600 mg q.d.)	Diltiazem: AUC: ↓ 69 % (↓ 55 to ↓ 79) C_{max}: ↓ 60 % (↓ 50 to ↓ 68) C_{min}: ↓ 63 % (↓ 44 to ↓ 75) Desacetyl diltiazem: AUC: ↓ 75 % (↓ 59 to ↓ 84) C_{max}: ↓ 64 % (↓ 57 to ↓ 69) C_{min}: ↓ 62 % (↓ 44 to ↓ 75) N-monodesmethyl diltiazem:	Dose adjustments of diltiazem when co-administered with **CITENVIR** should be guided by clinical response (refer to the Professional Information for diltiazem).

	AUC: ↓ 37 % (↓ 17 to ↓ 52) C_{max}: ↓ 28 % (↓ 7 to ↓ 44) C_{min}: ↓ 37 % (↓ 17 to ↓ 52) Efavirenz: AUC: ↑ 11 % (↑ 5 to ↑ 18) C_{max}: ↑ 16 % (↑ 6 to ↑ 26) C_{min}: ↑ 13 % (↑ 1 to ↑ 26) (CYP3A4 induction) The increase in efavirenz pharmacokinetic parameters is not considered clinically significant.	
Diltiazem/Emtricitabine	Interaction not studied.	
Diltiazem/Tenofovir disoproxil	Interaction not studied.	
Verapamil, Felodipine, Nifedipine and Nicardipine	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil. When efavirenz is co-administered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme, there is	Dose adjustments of calcium channel blockers when co-administered with **CITENVIR** should be guided by clinical response (refer to the Professional Information for the calcium channel blocker).

	a potential for reduction in the plasma concentrations of the calcium channel blocker.	
LIPID LOWERING MEDICINAL PRODUCTS		
HMG Co-A Reductase Inhibitors		
Atorvastatin/Efavirenz (10 mg q.d./600 mg q.d.)	Atorvastatin: AUC: ↓ 43 % (↓ 34 to ↓ 50) C_{max}: ↓ 12 % (↓ 1 to ↓ 26) 2-hydroxy atorvastatin: AUC: ↓ 35 % (↓ 13 to ↓ 40) C_{max}: ↓ 13 % (↓ 0 to ↓ 23) 4-hydroxy atorvastatin: AUC: ↓ 4 % (↓ 0 to ↓ 31) C_{max}: ↓ 47 % (↓ 9 to ↓ 51) Total active HMG Co-A reductase inhibitors: AUC: ↓ 34 % (↓ 21 to ↓ 41) C_{max}: ↓ 20 % (↓ 2 to ↓ 26)	Cholesterol levels should be periodically monitored. Dosage adjustments of atorvastatin may be required when co-administered with **CITENVIR** (refer to the Professional Information for atorvastatin).
Atorvastatin/Emtricitabine	Interaction not studied.	

Atorvastatin/Tenofovir disoproxil	Interaction not studied.	
Pravastatin/Efavirenz (40 mg q.d./600 mg q.d.)	Pravastatin: AUC: ↓ 40 % (↓ 26 to ↓ 57) C_{max}: ↓ 18 % (↓ 59 to ↑ 12)	Cholesterol levels should be periodically monitored. Dosage adjustments of pravastatin may be required when co-administered with **CITENVIR** (refer to the Professional Information for pravastatin).
Pravastatin/Emtricitabine	Interaction not studied.	
Pravastatin/Tenofovir disoproxil	Interaction not studied.	
Simvastatin/Efavirenz (40 mg q.d./600 mg q.d.)	Simvastatin: AUC: ↓ 69 % (↓ 62 to ↓ 73) C_{max}: ↓ 76 % (↓ 63 to ↓ 79) Simvastatin acid: AUC: ↓ 58 % (↓ 39 to ↓ 68) C_{max}: ↓ 51 % (↓ 32 to ↓ 58) Total active HMG Co-A reductase inhibitors: AUC: ↓ 60 % (↓ 52 to ↓ 68) C_{max}: ↓ 62 % (↓ 55 to ↓ 78) (CYP3A4 induction)	Cholesterol levels should be periodically monitored. Dosage adjustments of simvastatin may be required when co-administered with **CITENVIR** (refer to the Professional Information for simvastatin).

	Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values.	
Simvastatin/Emtricitabine	Interaction not studied.	
Simvastatin/Tenofovir disoproxil	Interaction not studied.	
Rosuvastatin/Efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces, therefore interaction with efavirenz is not expected.	**CITENVIR** and rosuvastatin can be co-administered without dose adjustment.
Rosuvastatin/Emtricitabine	Interaction not studied.	
Rosuvastatin/Tenofovir disoproxil	Interaction not studied.	
HORMONAL CONTRACEPTIVES		
Oral: Ethinyloestradiol+ Norgestimate/Efavirenz (0.035 mg+0.25 mg q.d./600 mg q.d.)	Ethinyloestradiol: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 8 % (↑ 14 to ↓ 25) Norelgestromin (active metabolite): AUC: ↓ 64 % (↓ 62 to ↓ 67) C_{max}: ↓ 46 % (↓ 39 to ↓ 52) C_{min}: ↓ 82 %	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).

	(↓ 79 to ↓ 85) Levonorgestrel (active metabolite): AUC: ↓ 83 % (↓ 79 to ↓ 87) C_{max}: ↓ 80 % (↓ 77 to ↓ 83) C_{min}: ↓ 86 % (↓ 80 to ↓ 90) (induction of metabolism) Efavirenz: no clinically significant interaction. The clinical significance of these effects is not known.	
Ethinyloestradiol/ Tenofovir disoproxil (-/245 mg q.d.)	Ethinyloestradiol: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Norgestimate/ Ethinyloestradiol/ Emtricitabine	Interaction not studied.	
Injection: Depomedroxy-progesterone acetate (DMPA)/Efavirenz	In a 3-month drug interaction study, no significant differences in MPA pharmacokinetic parameters were found between subjects	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).

(150 mg IM single dose DMPA)	receiving efavirenz-containing antiretroviral therapy and subjects receiving no antiretroviral	
DMPA/Emtricitabine	Interaction not studied.	
DMPA/Tenofovir disoproxil	Interaction not studied.	
Implant: Etonogestrel/Efavirenz	Decreased exposure of etonogestrel maybe expected (CYP3A4 induction). There have been occasional post-marketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
Ethonogestrel/emtricitabine	Interaction not studied.	
Ethonogestrel/tenofovir disoproxil	Interaction not studied.	
IMMUNOSUPRESSANTS		
Immunosuppressants metabolised byCYP3A4 (e.g. cyclosporine, tacrolimus, sirolimus) /Efavirenz	Interaction not studied. ↓ exposure of the immunosuppressant may be expected (CYP3A4 induction). These immunosuppressants are not anticipated to impact exposure of efavirenz.	Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least two weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with **CITENVIR**.
Tacrolimus/Emtricitabine/ Tenofovir disoproxil	Tacrolimus: AUC: ↔	

(0.1 mg/kg q.d./200 mg/245 mg q.d.)	C_{max}: ↔ C24h: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C24h: ↔ Tenofovir disoproxil: AUC: ↔ C_{max}: ↔ C24h: ↔	
OPIOIDS		
Methadone/Efavirenz (35-100 mg q.d./600 mg q.d.)	Methadone: AUC: ↓ 52 % (↓ 33 to ↓ 66) C_{max}: ↓ 45 % (↓ 25 to ↓ 59) (CYP3A4 induction) In a study of HIV infected intravenous drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms.	Concomitant administration with **CITENVIR** should be avoided due to the risk for QTc prolongation (see section 4.3).

Methadone/Tenofovir disoproxil (40-110 mg q.d./245 mg q. d.)	Methadone: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	
Methadone/Emtricitabine	Interaction not studied.	
Buprenorphine/naloxone/ Efavirenz	Buprenorphine: AUC: ↓ 50 % Norbuprenorphine: AUC: ↓ 71 % 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 **CITENVIR**.
Buprenorphine/naloxone/ Emtricitabine	Interaction not studied.	
Buprenorphine/naloxone/ Tenofovir disoproxil	Interaction not studied.	

[1]The predominant circulating metabolite of sofosbuvir.

Efavirenz Assay Interference

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy should be avoided in women receiving **CITENVIR**.

Women of childbearing potential should undergo pregnancy testing before initiation of **CITENVIR**.

Contraceptive 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 **CITENVIR**. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of **CITENVIR** is recommended.

Pregnancy

CITENVIR should not be used during pregnancy (see section 4.3).

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving **CITENVIR**. If **CITENVIR** is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking **CITENVIR**, the patient should be informed of the potential harm to the foetus.

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

Efavirenz: Birth defects may occur.

Breastfeeding

It is recommended that HIV-infected mothers do not breast-feed their infants to avoid risking post-natal transmission of HIV.

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

Efavirenz, emtricitabine and tenofovir have been shown to be excreted in human milk.

Fertility

No human data on the effect of **CITENVIR** are available.

4.7 Effects on ability to drive ad use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness has been reported during treatment with efavirenz, emtricitabine and tenofovir disoproxil. Efavirenz may also cause impaired concentration and/or somnolence.

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

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions were psychiatric disorders, nervous system disorders and gastrointestinal disorders.

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 **CITENVIR** (see section 4.4).

Discontinuation of **CITENVIR** 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 **CITENVIR** with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

The adverse reactions from clinical study and post-marketing experience and the individual components of **CITENVIR** in antiretroviral combination therapy are listed in the table below by body system organ class, frequency and the components of **CITENVIR** to the which the adverse reactions are attributable. Within each frequency grouping undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as frequent, less frequent and frequency unknown.

b. Tabulated list of adverse reactions

	CITENVIR		
	Efavirenz	**Emtricitabine**	**Tenofovir disoproxil**
Blood and lymphatic system disorders			
Frequent		neutropenia	
Less frequent		anaemia[1]	
Immune system disorders			
Frequent		allergic reaction	
Less frequent	hypersensitivity		
Metabolism and nutritional disorders			
Frequent	hypertriglyceridaemia[3]	hypertriglyceridaemia hyperglycaemia	hypophosphataemia[2]
Less frequent	hypercholesterolaemia		hypokalaemia lactic acidosis
Psychiatric disorders			
Frequent	depression[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[3] headache[3] disturbance in attention[3] dizziness[3]	headache dizziness	headache dizziness
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 pancreatic amylase elevated serum lipase vomiting abdominal pain dyspepsia	diarrhoea vomiting nausea abdominal pain abdominal distension flatulence
Less frequent	pancreatitis		pancreatitis
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[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 kinase	
Less frequent			rhabdomyolysis muscular weakness 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) 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 considered to be casually 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.

Description of selected adverse reactions

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. **CITENVIR** can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when **CITENVIR** is restarted.

Psychiatric symptoms: Patients with a history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions listed under efavirenz.

Nervous system symptoms: Nervous system symptoms are common with efavirenz, one of the components of **CITENVIR**. 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 **CITENVIR** is taken concomitantly with meals possibly due to increased efavirenz plasma levels. 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 were sometimes characterised by a fulminant course, progressing in some cases to transplantation or death.

Renal impairment: As **CITENVIR** may cause renal damage, monitoring of renal function is recommended (see section 4.4 and section 4.8). 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 medications) 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 medications 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).

Paediatric population

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

Other special populations

Elderly: CITENVIR 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 **CITENVIR**.

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 **CITENVIR** (see section 4.2 and, section 4.4).

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

If overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of the patient's clinical status, standard supportive treatment should then be applied as necessary. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. Haemodialysis can remove both emtricitabine and tenofovir DF (refer to detailed information below) but is unlikely to significantly remove efavirenz from the blood.

Efavirenz: Some patients taking 600 mg twice daily have reported increased nervous system symptoms.

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

CITENVIR is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz is a non-nucleoside reverse transcriptase inhibitor; emtricitabine is a synthetic nucleoside analogue of cytidine and tenofovir DF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleoside) analogue of adenosine 5'-monophosphate.

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

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

Tenofovir disoproxil fumarate: Tenofovir DF is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of

HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

Antiviral Activity

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

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

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

Tenofovir disoproxil fumarate: The antiviral activity in cell culture of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral

blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0,04 to 8,5 µm. In medicine combination studies of tenofovir with NRTIs (abacavir, didanosine, lamivudine, stavudine, zalcitabine and zidovudine), NNRTIs (delavirdine, efavirenz and nevirapine), and PIs (amprenavir, indinavir, nelfinavir, ritonavir and saquinavir), additive to synergistic effects were reported. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC_{50} values ranged from 0,5 to 2,2 µm) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1,6 µm to 4,9 µm).

Resistance

Efavirenz, emtricitabine, and tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT.

Genotypic analysis of the resistant isolated showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Cross-resistance

Efavirenz, emtricitabine and tenofovir disoproxil fumarate: Cross-resistance has been recognised among NNRTIs. Cross resistance has also been recognised among certain NRTIs. The M184V/I and/or K65R substitutions selected in cell culture by the combination of emtricitabine and tenofovir are also reported in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours either, or both of these amino acid substitutions.

5.2 Pharmacokinetic properties

Efavirenz: In HIV-infected patients time-to-peak plasma concentrations are approximately 3 to 5 hours and steady-state plasma concentrations are reached in 6 to 10 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state C_{max} was 12,9 ± 3,7 µm (mean ± SD), C_{min} was 5,6 ± 3,2 µm, and AUC was 184 ± 73 µm-hr. Efavirenz is highly bound (approximately 99,5 to 99,75 %) to human plasma proteins, predominantly albumin. Following administration of ^{14}C-labelled efavirenz, 14 to 34 % of the dose is recovered in the urine (mostly as metabolites) and

16 to 61 % is recovered in faeces (mostly as parent medicine). *In vitro* studies suggest CYP3A4 and CYP2B6 are the major isoenzymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52 to 76 hours after single doses, and 40 to 55 hours after multiple doses.

Emtricitabine: Following oral administration, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-infected subjects, the steady-state plasma emtricitabine C_{max} was 1,8 ± 0,7 µg/mL (mean ± SD) and the AUC over a 24-hour dosing interval was 10,0 ± 3,1 µg hr/mL. The mean steady state plasma trough concentration at 24 hours post-dose was 0,09 µg/mL. The mean absolute bioavailability of emtricitabine was 93 %. *In vitro* binding of emtricitabine to human plasma proteins is less than 4 % and is independent of concentration over the range of 0,02 to 200 µg/mL. Following administration of radio-labelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 213 ± 89 mL/min (mean ± SD).

Following a single oral dose, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate: Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1,0 ± 0,4 hours (mean ± SD) and C_{max} and AUC values were 296 ± 90 ng/mL and 2,287 ± 685 ng hr/mL, respectively. The oral bioavailability of tenofovir from tenofovir DF in fasted patients is approximately 25 %. *In vitro* binding of tenofovir to human plasma proteins is less than 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/mL. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of food on oral absorption

CITENVIR has not been evaluated in the presence of food.

Administration of efavirenz tablets with a high fat meal increased the mean AUC and C_{max} of efavirenz by 28 % and 79 %, respectively, compared to administration in the fasted state. Compared to fasted administration, dosing of

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

Special Populations

Paediatric and elderly patients

Pharmacokinetic studies of tenofovir DF have not been performed in paediatric patients (less than 18 years). Efavirenz has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg. Emtricitabine has been studied in paediatric patients from 3 months to 17 years of age. **CITENVIR** is not recommended for paediatric administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir has not been fully evaluated in the elderly (more than 65 years).

Patients with impaired renal function

Efavirenz: The pharmacokinetics of efavirenz has not been studied in patients with renal insufficiency, however, less than 1 % of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Emtricitabine and tenofovir disoproxil fumarate: The pharmacokinetics of emtricitabine and tenofovir DF are altered in patients with renal impairment. In patients with creatinine clearance less than 50 mL/min, C_{max} and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased (see section 4.3 and section 4.5, Renal impairment).

Patients with hepatic impairment

Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see section 4.5).

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients of **CITENVIR** are croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, opadry II white and sodium lauryl sulphate.

Opadry II white contains macrogol, polyvinyl alcohol, talc and titanium dioxide (C.I. No: 77891).

6.2 Incompatibilities

None.

6.3 Shelf life

24 months at or below 30 °C.

6.4 Special Precautions for storage

Store at or below 30 °C.

Keep HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and content of container

CITENVIR: HDPE Container Pack. Tablets are packed in white opaque round 100 mL HDPE container with 38 mm neck finish closed with 38 mm-400 CR white opaque polypropylene child resistant closure with wad having induction sealing liner. Each HDPE container shall contain a 3 g silica gel sachet.

Pack size: 30’s. One HDPE container contains 30 tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd

Office 2, 100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene – Pretoria

South Africa

8. REGISTRATION NUMBER

47/20.2.8/0504

9. DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 June 2013

10. DATE OF REVISION OF THE TEXT

05 January 2022

FOR NAMIBIA ONLY:

Schedule: NS2

Registration Number:

Citenvir: 13/20.2.8/0240