1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

TRIBUSS (film-coated tablet)

COMPOSITION

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

Excipients:

Black iron oxide (C.I. 77499), croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, red iron oxide (C.I. 77491), sodium lauryl sulphate, talc, titanium dioxide (C.I. 77891).

Contains sugar: Lactose monohydrate 120,0 mg

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES SUCH AS TRIBUSS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (see WARNINGS AND SPECIAL PRECAUTIONS). TRIBUSS IS NOT INDICATED FOR THE

TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TRIBUSS HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED TRIBUSS. 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 WHO DISCONTINUE THE COMBINATION TABLET. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (see WARNINGS AND SPECIAL PRECAUTIONS).

CATEGORY AND CLASS

A 20.2.8 Antiviral Agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

Mechanism of Action

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate also known as tenofovir DF is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir disoproxil fumarate 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 Reverse Transcriptase (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 polymerasesα,β and mitochondrial DNA polymeraseγ.

Efavirenz

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Efavirenz is a non-competitive inhibitor of (HIV-1) reverse transcriptase (RT) with respect to template, primer or nucleoside triphosphates, with a small component of competitive inhibition. HIV-2 RT and human cellular DNA polymerases alpha, beta, gamma and delta are not inhibited by concentrations of 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 reverse transcriptase (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 polymeraseα,β ε and mitochondrial DNA polymeraseγ.

Resistance

Tenofovir disoproxil fumarate, efavirenz and emtricitabine

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in *in vitro* cell culture and in clinical studies. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT, as well as the K103N substitution.

In a clinical study of treatment-naïve patients (emtricitabine + tenofovir DF + efavirenz versus zidovudine + lamivudine + efavirenz), resistance analysis was performed on HIV isolates from all virologic failure patients with >400 copies/ml of HIV-1 RNA at Week 48 or early discontinuations. Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Development of efavirenz resistance-associated mutations occurred most frequently and was similar between the treatment arms.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/12 (17 %) analysed patient isolates in the emtricitabine + tenofovir group and in 7/22 (32 %) analysed patient isolates in the zidovudine/lamivudine group. Through 48 weeks, no patient has developed a detectable K65R mutation in their HIV as analysed through standard genotypic analysis. Insufficient data are available to assess the development of the K65R mutation upon prolonged exposure to this regimen.

In treatment-naïve patients, 8/47 (17 %) isolates from patients on tenofovir DF developed the K65R substitution through week 144 of therapy, 7 of these occurred in the first 48 weeks of treatment and one at week 96. In treatment-experienced patients, 14/304 (5 %) isolates from patients failing tenofovir through week 96 showed >1, 4 fold (median 2, 7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Tenofovir disoproxil fumarate

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in *in vitro* cell culture. These viruses expressed a K65R mutation in RT and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

Efavirenz

Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. The most frequently observed amino acid substitution in clinical studies with efavirenz is K103N (54 %). One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, 227 and 230 were observed in patients failing treatment with efavirenz in combination with other antiretrovirals. Other resistance mutations observed to emerge commonly included L100I (7 %), K101E/Q/R (14 %), V108I (11 %), G190S/T/A (7 %), P225H (18 %) and M230I/L (11 %).

HIV‑1 isolates with reduced susceptibility to efavirenz (more than 380-fold increase in EC_{90} value) emerged rapidly under selection in cell culture. Genotypic characterisation of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I and triple substitutions L100I/V179D/Y181C in RT.

Emtricitabine

Emtricitabine-resistant isolates of HIV have been selected in *in vitro* cell culture and *in vivo*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Cross-resistance

Tenofovir disoproxil fumarate, efavirenz and emtricitabine

Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognised. Cross-resistance has also been recognised among non-nucleoside reverse transcriptase inhibitors (NNRTIs). The M184V/I and/or K65R substitutions selected in *in vitro* cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours either or both of these amino acid substitutions.

Emtricitabine

Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility in *in vitro* cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine.

Tenofovir disoproxil fumarate

The K65R mutation selected by tenofovir is also selected in some HIV-1 infected patients treated with abacavir, didanosine or zalcitabine. HIV-1 isolates with the K65R mutation also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours the K65R mutation.

HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3'-zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) showed a 3,1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Efavirenz

Clinical isolates previously characterised as efavirenz-resistant were also phenotypically resistant in cell culture to delavirdine and nevirapine compared to baseline. Delavirdine- and/or nevirapine-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L or M230L) showed reduced susceptibility to efavirenz in cell culture. Greater than 90 % of NRTI-resistant isolates tested in cell culture retained susceptibility to efavirenz.

Antiviral activity

Tenofovir disoproxil fumarate, efavirenz and emtricitabine

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

Tenofovir disoproxil fumarate

The antiviral activity 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 nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine,

zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC_{50} values ranged from 0,5 to 2,2 µM). The EC_{50} values of tenofovir against HIV-2 ranged from 1,6 µM to 4,9 µM.

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, zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these medicine combinations have not been studied in humans. Emtricitabine displayed antiviral activity in *in vitro* 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).

Pharmacokinetic properties

Pharmacokinetics in adults

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 hrs (mean ± SD), and C_{max} and AUC values were 296 ± 90 ng/ml and 2287 ± 685 ng.hr/ml, respectively.

The oral bioavailability of tenofovir from tenofovir DF in fasted patients is approximately 25 %.

In vitro binding of tenofovir to human plasma proteins is <0, 7 % and is independent of concentration over the range of 0, 01 to 25 µg/ml.

Approximately 70 % to 80 % of the intravenous dose of tenofovir is recovered as unchanged medicine in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 ml/min (mean ± SD).

Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Efavirenz

In HIV-infected patients time-to-peak plasma concentrations were approximately 3 to 5 hours and steady-state plasma concentrations were 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 was recovered in the urine (mostly as metabolites) and 16 % - 61 % was recovered in faeces (mostly as parent medicine). *In vitro* studies suggest CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce P450 enzymes, resulting in 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 of emtricitabine (200 mg), 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.

In *in vitro* cell culture, binding of emtricitabine to human plasma proteins is <4 % and is independent of concentration over the range of 0, 02 to 200 µg/ml.

Following administration of radiolabelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 213 ± 89 ml/min (mean ± SD). Following a single oral dose of emtricitabine (200 mg), the plasma emtricitabine half-life is approximately 10 hours.

Effects of Food on Oral Absorption

TRIBUSS has not been evaluated in the presence of food.

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

Compared to fasted administration, dosing of tenofovir DF and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35 % and 15 %, respectively, without affecting emtricitabine exposures (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS).

Special populations

Paediatrics

TRIBUSS is not recommended for paediatric administration as the combination has not been studied in this age group (see CONTRAINDICATIONS).

Elderly

Pharmacokinetics of tenofovir, efavirenz and emtricitabine has not been fully evaluated in the elderly (>65 years) (see WARNINGS AND SPECIAL PRECAUTIONS, Elderly use).

Patients with impaired renal function

Tenofovir disoproxil fumarate and emtricitabine

The pharmacokinetics of tenofovir DF and emtricitabine are altered in patients with renal impairment.

In patients with creatinine clearance of <50 ml/min, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were significantly increased (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS, Renal impairment).

Efavirenz

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

Patients with hepatic impairment

The pharmacokinetics of efavirenz have not been studied in patients with hepatic impairment (see WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS

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

CONTRAINDICATIONS

TRIBUSS is contraindicated in:

- Patients with a known hypersensitivity to tenofovir, emtricitabine, efavirenz or any of the excipients of TRIBUSS (see COMPOSITION).
- Patients with moderate (creatinine clearance 30 to 50 ml/min) or severe renal impairment (creatinine clearance < 30 ml/min (CrCl)). Patients with moderate or

severe renal impairment require dose adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with TRIBUSS (see WARNINGS AND SPECIAL PRECAUTIONS).

- Concomitant use with bepridil, cisapride, midazolam, pimozide, terfenadine, triazolam or ergot derivatives, because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g. cardiac dysrhythmias, prolonged sedation, or respiratory depression) (see INTERACTIONS).
- Concomitant use with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see INTERACTIONS).
- Concomitant use with St John's Wort (Hypericum perforatum).
- Patients with a history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART).
- Patients with severe hepatic impairment (see WARNINGS AND SPECIAL PRECAUTIONS).
- Children less than 18 years of age, due to lack of data on safety and efficacy.
- Pregnancy and lactation (see HUMAN REPRODUCTION).

WARNINGS AND SPECIAL PRECAUTIONS

Patients with hepatic impairment

Liver enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medicines associated with liver toxicity, monitoring of liver enzymes is recommended.

In patients with persistent elevations of serum transaminases to greater than five

times the upper limit of the normal range, the benefit of continued therapy with TRIBUSS needs to be weighed up against the unknown risks of significant liver toxicity (see SIDE EFFECTS).

Tenofovir disoproxil fumarate

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

Efavirenz

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

Patients on TRIBUSS 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 TRIBUSS or efavirenz containing medicines should be stressed. Patients who discontinued treatment with TRIBUSS should be followed up for symptoms/signs of

liver failure for up to 12 months.

TRIBUSS is contraindicated in patients with moderate to severe hepatic impairment (see CONTRAINDICATIONS).

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

Emtricitabine

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

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals, such as in TRIBUSS. 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. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality rate and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with TRIBUSS should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

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

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

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

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

Co-administration with related medicines (*see INTERACTIONS*)

As a fixed combination, TRIBUSS should not be administered concomitantly with other medicines containing any of the same active components, namely: tenofovir disoproxil fumarate, efavirenz or emtricitabine.

Due to similarities with emtricitabine, TRIBUSS should not be administered concomitantly with other cytidine analogues, such as lamivudine, including the lamivudine/zidovudine combination, or the abacavir sulphate/lamivudine combination, or the abacavir sulphate/lamivudine/zidovudine combination.

Patients co-infected with HIV and Hepatitis B Virus

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. TRIBUSS is not indicated for the treatment of chronic HBV infection and the safety and efficacy of TRIBUSS have not been established in patients co-infected with HBV and HIV. Discontinuation of TRIBUSS therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued the emtricitabine 200 mg/tenofovir 300 mg combination or tenofovir DF 300 mg alone. In some of these patients the exacerbations of hepatitis B were associated with liver decompensation and liver failure.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are co- infected with HIV and HBV and discontinue TRIBUSS. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal impairment

Tenofovir and emtricitabine are principally eliminated by the kidney; however, efavirenz is not. Since TRIBUSS is a combination medicine and the dose of the individual components cannot be altered, patients with creatinine clearance <50 ml/min should not receive TRIBUSS (see CONTRAINDICATIONS).

$$\text{*eGFR (ml/min)} = \frac{140\text{-age (years)} \times \text{weight (kg)}}{\text{serum creatinine (µmol/l)}}$$

*eGFR (estimated glomerular filtration rate)

For females multiply the GFR by 0,85

Renal impairment, including cases of acute renal failure and Fanconi syndrome

(renal tubular injury with severe hypophosphataemia), has been reported in association with the use of tenofovir DF (see CONTRAINDICATIONS and SIDE EFFECTS).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with TRIBUSS.

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment (see CONTRAINDICATIONS and SIDE EFFECTS).

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

Psychiatric symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. There have been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweighs the benefits (see SIDE EFFECTS).

Nervous system symptoms

Fifty-three percent of patients receiving efavirenz in controlled trials reported central nervous system symptoms compared to 25 % of patients receiving control regimens. These symptoms included dizziness (28, 1 %), insomnia (16, 3 %),

impaired concentration (8, 3 %), somnolence (7, 0 %), abnormal dreams (6, 2 %), and hallucinations (1, 2 %). Other reported symptoms were euphoria, confusion, agitation, amnesia, stupor, abnormal thinking and depersonalisation. The majority of these symptoms were mild-to-moderate (50, 7 %); symptoms were severe in 2, 0 % of patients. Overall 2, 1 % of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5 % to 9 % in patients treated with regimens containing efavirenz and from 3 % to 5 % in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms (see WARNINGS AND SPECIAL PRECAUTIONS, Psychiatric symptoms).

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

Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Caution must be taken in any patient with a history of seizures.

Patients who are receiving concomitant anticonvulsant medicines primarily metabolised by the liver, such as phenytoin and phenobarbitone may require periodic monitoring of plasma levels.

Animal Toxicology: Non-sustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4 to 13 fold greater than

those in humans given the recommended dose.

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 TRIBUSS. 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 TRIBUSS.

If TRIBUSS is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking TRIBUSS, the patient should be informed of the potential harm to the foetus (see CONTRAINDICATIONS AND HUMAN REPRODUCTION).

Paediatric use

TRIBUSS 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 (see CONTRAINDICATIONS).

Elderly use

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

Bone effects

Tenofovir disoproxil fumarate: In a study of treatment naïve patients, decreases in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. There was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir + lamivudine + efavirenz compared with patients receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the study and this reduction was sustained through Week 144.

Twenty-eight percent (28 %) of tenofovir-treated patients vs. 21 % of the stavudine-treated patients lost at least 5 % of BMD at the spine or 7 % of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide) in the tenofovir group relative to the stavudine group, suggesting increased bone turnover.

Serum parathyroid hormone levels and 1, 25 Vitamin D levels were also higher in the tenofovir group relative to the stavudine group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

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

Bone monitoring should be considered for HIV infected patients who have a history

of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

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.

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, elevated serum lipid and glucose levels in HIV patients and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Skin rash

In a study of patients treated with 600 mg efavirenz more patients experienced

new-onset skin rash compared with the patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0, 9 % of patients treated with efavirenz.

The incidence of Grade 4 rash (e.g. erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0, 1 %. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days).

The discontinuation rate for rash was 1, 7 %.

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

Experience with efavirenz in patients who discontinued other antiretroviral medicines of the NNRTI class is limited. Of nineteen patients who discontinued nevirapine because of rash and who were treated with efavirenz, nine developed mild to moderate rash, and two of these patients discontinued because of rash.

Immune reconstitution syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically,

such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

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

Effects on ability to drive and use machines:

TRIBUSS may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should

avoid potentially hazardous tasks such as driving or operating machinery.

Excipients

Lactose warning

TRIBUSS contains lactose which may have an effect on the glycemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take TRIBUSS.

INTERACTIONS

No medicine interaction studies have been conducted using TRIBUSS film-coated tablets. As TRIBUSS contains tenofovir disoproxil fumarate, efavirenz, and emtricitabine, any interactions that have been identified with these medicines individually may occur with TRIBUSS.

Efavirenz

Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz.

In vitro studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with medicines primarily metabolised by these isozymes may result in altered plasma concentrations of the co-administered medicine. Therefore, appropriate dose adjustments may be necessary for these medicines.

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

Emtricitabine and tenofovir disoproxil fumarate

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TRIBUSS with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir and/or other renally eliminated medicines. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir and valganciclovir.

Co-administration of tenofovir DF and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events (for didanosine dosing adjustment recommendations, see Table 2 in the INTERACTIONS section).

Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily.

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

TRIBUSS should be discontinued in patients who develop tenofovir-associated adverse events (for atazanavir dosing adjustment recommendations (see Table 2

in the INTERACTIONS section).

Other important medicine interaction information for TRIBUSS is summarised in Table 1 and 2. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual medicines or are potential medicine interactions; no medicine interaction studies have been conducted using TRIBUSS. The tables include potentially significant interactions, but are not all inclusive.

Table 1

Medicines that are contraindicated or not recommended for use with TRIBUSS

Medicine Class: **Medicine Name**	**Clinical Comment:**
Antifungal: voriconazole	Contraindicated because efavirenz significantly decreases voriconazole plasma concentrations, and co-administration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects.
Antihistamine: astemizole	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

Antimigraine: Ergot derivatives	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.
Antiretrovirals: emtricitabine, tenofovir, efavirenz, lamivudine.	Not for use with TRIBUSS because emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz are components of TRIBUSS. Lamivudine is similar to emtricitabine.
Benzodiazepines: midazolam, triazolam	Contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
GI motility medicines: cisapride	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Neuroleptic: pimozide	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
St. John's wort *(Hypericum perforatum)*	Not recommended: Expected to substantially decrease plasma levels of efavirenz; has not been studied in

	combination with efavirenz.

Table 2

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

Concomitant Medicine Class: Medicine Name	**Effect**	**Clinical Comment**
Antiretroviral agents		
Protease inhibitor: amprenavir	↓ amprenavir concentration	Efavirenz has the potential to decrease serum concentrations of amprenavir
Protease inhibitor: fosamprenavir calcium	↓ fosamprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and TRIBUSS with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when TRIBUSS is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when TRIBUSS is administered with fosamprenavir plus ritonavir twice daily.

Protease inhibitor: atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Plasma concentrations of atazanavir were decreased by both efavirenz and tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with TRIBUSS. Therefore, co-administration of TRIBUSS and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations.
Protease inhibitor: indinavir	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1 000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: lopinavir/ ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **Patients should be monitored for tenofovir-associated adverse events. TRIBUSS should be discontinued in**

		patients who develop tenofovir-associated adverse events.
Protease inhibitor: ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours was co-administered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g. dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when TRIBUSS is used in combination with ritonavir.
Protease inhibitor: saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with TRIBUSS.
NRTI: didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. **In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg if co-administered with TRIBUSS. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg.** When co-administered, TRIBUSS and didanosine must be taken under fasted conditions or with a light meal (<400 kcal, 20 %

		fat). Co-administration of didanosine buffered formulation with TRIBUSS should be under fasted conditions. **Co-administration of TRIBUSS and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. For additional information, please consult the didanosine prescribing information.**
Other agents:		
Anticoagulant: warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects (INR) potentially increased or decreased by efavirenz.
Anticonvulsants: carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for TRIBUSS. Alternative anticonvulsant treatment should be used.
Anticonvulsants: Phenytoin phenobarbital	↓ Anticonvulsant concentration ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.

	concentration	
Antidepressant: sertraline	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Antifungals: itraconazole ketoconazole	↓ itraconazole[1] concentration ↓ hydroxy-itraconazole[1] concentration ↓ ketoconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered. Medicine interaction studies with TRIBUSS and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Anti-infective: clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46 % developed rash while receiving efavirenz and clarithromycin. No dose adjustment of TRIBUSS is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with TRIBUSS.
Antimycobacterial: rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50 %. Consider doubling the rifabutin dose in regimens where rifabutin is

		given 2 or 3 times a week.
Antimycobacterial: rifampicin	↓ efavirenz[1] concentration	Clinical significance of reduced efavirenz concentration is unknown. Dosing recommendations for concomitant use of TRIBUSS and rifampicin have not been established.
Calcium channel blockers: diltiazem	↓ diltiazem[1] concentration ↓ desacetyl diltiazem[1] concentration ↓ N-monodesmethyl diltiazem[1] concentration	Diltiazem dose adjustments should be guided by clinical response (refer to the complete prescribing information for diltiazem). No dose adjustment of TRIBUSS.
Others (e.g. felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the complete prescribing information for the calcium channel blocker).

HMG-CoA reductase inhibitors: atorvastatin pravastatin simvastatin	↓ atorvastatin[1] concentration ↓ pravastatin[1] concentration ↓ simvastatin[1] concentration	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased with efavirenz. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualising the dose.
Narcotic analgesic: methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-infected individuals with a history of injection medicine use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Oral contraceptive: ethinyl oestradiol	↑ ethinyl oestradiol concentration	Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception should be used in addition to oral contraceptives.

1. This list is not conclusive

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 who received efavirenz. False-positive test results have only been observed with the Microgenics Cedia DAU Multi-Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

Other Interactions

Efavirenz

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

Emtricitabine and tenofovir disoproxil fumarate

No clinically significant medicine interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir DF and zidovudine. Similarly, no clinically significant medicine interactions have been observed between tenofovir DF and abacavir, adefovir dipivoxil, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin and saquinavir/ritonavir in studies conducted in healthy volunteers.

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy, oral contraceptives or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant medicine interactions between these medicines and tenofovir DF.

HUMAN REPRODUCTION

Pregnancy

TRIBUSS should not be used in pregnancy (see CONTRAINDICATIONS).

Efavirenz may cause foetal harm when administered during the first trimester of pregnancy. Pregnancy should be avoided in women receiving TRIBUSS. A reliable form of barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives) while on therapy with TRIBUSS.

Women should be advised to notify their medical practitioner or health care professional if they plan to become pregnant while taking TRIBUSS. If TRIBUSS is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking TRIBUSS, she should be informed of the potential harm to the foetus.

Women of childbearing potential should undergo pregnancy testing before initiation of TRIBUSS.

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

Lactation

Breastfeeding mothers: HIV-infected mothers should not breastfeed their infants, to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that both efavirenz and tenofovir are secreted in milk.

It is not known whether tenofovir, emtricitabine or efavirenz is excreted in human milk. 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 TRIBUSS.**

DOSAGE AND DIRECTIONS FOR USE

Adults

The dose of TRIBUSS is one tablet taken orally, once daily, on an empty stomach.

Dosing at bedtime may improve the tolerability to efavirenz with respect to undesirable effects on the nervous system.

Paediatrics and children

TRIBUSS is not recommended for use in patients <18 years of age.

Renal impairment

Because TRIBUSS is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate (creatinine clearance 30 to 50 ml/min) or severe renal impairment (creatinine clearance <30 ml/min) (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS, Renal impairment).

SIDE EFFECTS

Efavirenz

Immune system disorders

Less frequent: Allergic reactions

Frequency unknown: Immuno-allergic liver injury/failure

Endocrine disorders

Frequency unknown: Gynaecomastia

Metabolism and nutritional disorders

Less frequent: Anorexia, raised serum-cholesterol and triglyceride concentrations

Frequency unknown: Redistribution/accumulation of body fat, weight gain, weight loss, increased appetite.

Psychiatric disorders

Frequent: Aggravated depression

Less frequent: Abnormal dreams, anxiety, agitation, amnesia, apathy, confusion, emotional lability, euphoria, hallucination, insomnia, somnolence

Nervous system disorders

Frequent: Dizziness, headache

Less frequent: Impaired concentration, abnormal coordination, ataxia, convulsions, hypoaesthesia, paraesthesia, neuralgia, peripheral neuropathy, speech disorder,

tremor and vertigo, syncope

Eye disorder

Less frequent: Abnormal vision

Ear and labyrinth disorders

Less frequent: Tinnitus

Cardiac disorders

Less frequent: Palpitations and tachycardia

Respiratory, thoracic and mediastinal disorders

Less frequent: Asthma

Frequency unknown: Sinusitis, and upper respiratory tract infections

Gastrointestinal disorders

Frequent: Nausea

Less frequent: Vomiting, diarrhoea, dyspepsia, abdominal pain, taste perversion

Frequency unknown: Gastritis, gastroenteritis and gastro-oesophageal reflux, constipation, malabsorption

Hepato-biliary disorders

Less frequent: Hepatitis, hepatic enzyme increase

Frequency unknown: Hepatic failure

Skin and subcutaneous tissue disorders

Frequent: Rash and increased swelling

Less frequent: Erythema multiforme, Stevens-Johnson syndrome, alopecia, skin exfoliation, urticaria

Frequency unknown: Nail disorders, skin discolouration, acne, eczema, folliculosis, seborrhoea, photoallergic dermatitis

Musculoskeletal, connective tissue and bone disorders

Less frequent: Arthralgia, myalgia

Frequency unknown: Myopathy

Reproductive system and breast disorders

Frequency unknown: Impotence, decreased libido, increased libido

General disorders and administrative site conditions

Frequent: Fatigue

Less frequent: Asthenia, hot flushes, malaise

Frequency unknown: Influenza-like symptoms, pain

The type and frequency of side effects in children was generally similar to that of adult patients, with the exception that rash was reported more frequently in children and was more often of a higher grade than in adults.

Emtricitabine (200 mg)

Blood and lymphatic system disorders

Frequency unknown: Neutropenia, anaemia

Immune system disorders

Frequency unknown: Allergic reactions

Metabolism and nutrition disorders

Frequency unknown: Lactic acidosis – usually associated with severe hepatomegaly and steatosis, hypophosphatemia, hypertriglyceridemia, hyperglycaemia

Psychiatric disorders

Frequency unknown: Sleep disturbances (abnormal dreams, insomnia), depressive disorder

Nervous system disorders

Frequent: Headache

Frequency unknown: Dizziness, neuropathy, peripheral neuritis, paraesthesia

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Increased cough, rhinitis, dyspnoea

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea

Frequency unknown: Abdominal pain, dyspepsia, increased amylase, pancreatitis

Hepato-biliary disorders

Frequency unknown: Raised liver enzyme concentrations, hepatitis, hyperbilirubinemia

Skin and subcutaneous tissue disorders

Frequent: Rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction)

Frequency unknown: Skin discolouration – manifested by hyperpigmentation on the palms and/or soles, but is generally mild

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: Arthralgia, myalgia

Renal and urinary disorders

Frequent: Elevation of creatinine kinase

General disorders and administrative site conditions

Frequency unknown: Asthenia

Tenofovir (300 mg)

Blood and lymphatic system disorders

Frequency unknown: Neutropenia, haematuria

Immune system disorders:

Frequency unknown: Allergy, allergic reactions

Metabolism and nutrition disorders

Frequent: Hypophosphatemia

Frequency unknown: Lactic acidosis – usually associated with severe hepatomegaly and steatosis, hypertriglyceridemia, hyperglycaemia

Psychiatric disorders

Frequency unknown: Depression, insomnia, anxiety

Nervous system disorders

Frequency unknown: Headache, asthenia, dizziness, peripheral neuropathy (including peripheral neuritis and neuropathy)

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Chest pain, pneumonia, dyspnoea

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, abdominal pain, flatulence, dyspepsia and anorexia, weight loss

Less frequent: Raised serum amylase concentrations, pancreatitis

Frequency unknown: Abdominal pain

Hepato-biliary disorders

Frequency unknown: Raised liver enzymes, hepatitis

Skin and subcutaneous tissue disorders

Frequency unknown: Skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash),sweating

Musculoskeletal connective tissue and bone disorders

Frequency unknown: Back pain, myalgia, arthralgia, myopathy, osteomalacia

Renal and urinary disorders

Frequency unknown: Increased creatinine kinase levels, increased creatinine, interstitial nephritis, nephrogenic diabetes insipidus, polyuria, proximal tubulopathy, proteinuria, renal impairment, renal failure, renal insufficiency, acute renal failure, acute tubular necrosis, and effects on the renal proximal tubules, including Fanconi syndrome.

General disorders and administrative site conditions

Frequency unknown: Fever

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

Efavirenz

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms and involuntary muscle contractions

Tenofovir disoproxil fumarate

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

Emtricitabine

Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine (200 mg). In one clinical pharmacology study, single doses of emtricitabine 1 200 mg were administered to 11 patients. No severe adverse reactions were reported.

Treatment

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Efavirenz

Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status.

Administration of activated charcoal may be used to aid removal of unabsorbed

medicine. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the medicine from the blood.

Tenofovir

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.

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.

Treatment is symptomatic and supportive.

IDENTIFICATION

A pink coloured, capsule-shaped film-coated tablet debossed with “D100” on one side and plain on the other side.

PRESENTATION

28 or 30 or 84 tablets are packed in a white opaque wide mouth high density polyethylene container and sealed with a white opaque polypropylene cap together with a desiccant. The container is packed into an outer cardboard carton together

with a leaflet.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Keep the container tightly closed.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

44/20.2.8/0980

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Date of Registration: 25 November 2011

Date of the most recent amendment to the professional information as approved by Authority: 21 March 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn:

0800 118 088.

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