SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

ADCO EFAVIRENZ 50 mg capsule

ADCO EFAVIRENZ 100 mg capsule

ADCO EFAVIRENZ 200 mg capsule

ADCO EFAVIRENZ 600 mg film coated tablet

COMPOSITION:

ADCO EFAVIRENZ 50 mg:

Each capsule contains 50 mg efavirenz.

ADCO EFAVIRENZ 100 mg:

Each capsule contains 100 mg efavirenz.

ADCO EFAVIRENZ 200 mg:

Each capsule contains 200 mg efavirenz.

ADCO EFAVIRENZ 600 mg:

Each film coated tablet contains 600 mg efavirenz.

Inactive ingredients:

Hydroxypropylcellulose, lactose monohydrate, magnesium stearate, sodium lauryl sulphate.

ADCO EFAVIRENZ 50 mg, 100 mg and **200 mg** also contains gelatine, sodium starch glycolate, Opacode Black (containing iron oxide black (colourant), isopropyl alcohol, methylated spirit (industrial), N-Butyl alcohol, propylene glycol, purified water, shellac glaze).

ADCO EFAVIRENZ 600 mg also contains croscarmellose sodium, microcrystalline cellulose, Opadry II white (containing macrogol, polyvinyl alcohol-part hydrolysed, talc, titanium dioxide). Contains sugar (lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION:

A.20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Mechanism of action:

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Efavirenz diffuses into the cell where it binds adjacent to the active site of reverse transcriptase. This produces a conformational change in the enzyme and inhibits its function. 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.

Pharmacodynamic properties:

In vitro HIV susceptibility:

The clinical significance of in vitro susceptibility of HIV-1 to efavirenz has not been established. The in vitro antiviral activity of efavirenz was assessed in lymphoblastic cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The 90 to 95 % inhibitory concentration (IC90 to IC95) of efavirenz for wild type laboratory adapted strains and clinical isolates ranged from 1,7 to 25 nM.

Efavirenz demonstrated synergistic activity in cell culture in combination with the nucleoside analogue reverse transcriptase inhibitors (NRTIs), zidovudine (ZDV) or didanosine (ddi), or the protease inhibitor, indinavir (IDV).

Resistance:

HIV-1 isolates with reduced susceptibility to efavirenz (greater than 380-fold increase in IC90) compared to baseline can emerge in vitro. Phenotypic changes in evaluable HIV-1 isolates and genotypic changes in plasma virus from selected patients treated with efavirenz in combination with IDV or with ZDV plus lamivudine were monitored. One or more RT mutations at amino acid positions 100, 101, 103, 108, 190 and 225, were observed in all 62 patients with a frequency of at least 10 % compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagine) was the most frequently observed (greater or equal to 90 %). A mean loss in susceptibility (IC90) to efavirenz of 47-fold was observ**ed in 26 clinical** isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9 to greater than 312-fold increase in IC90) were observed for these isolates in vitro compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with efavirenz therapy has not been established.

Cross-resistance:

Rapid emergence of HIV-1 strains that are cross-resistant to non-nucleoside RT inhibitors has been observed in vitro. Clinical isolates previously characterised as efavirenz-resistant were also phenotypically resistant to nevirapine and delavirdine in vitro compared to baseline. Clinically derived ZDV-resistant HIV-1 isolated and tested in vitro retained susceptibility to efavirenz. Cross-resistance between efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Pharmacokinetic properties:

Absorption:

Peak efavirenz plasma concentrations of 1,6 to 9,1 µM were attained by 5 hours following single oral doses of 100 mg to 1 600 mg administered to uninfected volunteers. Dose-related increases in Cmax and AUC were seen for doses up to 1 600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

Steady state plasma concentrations are reached in 6 to 7 days.

Distribution:

Efavirenz is very highly bound (approximately 99,5 to 99,75 %) to human plasma proteins, predominantly albumin. In HIV-1 infected patients who received efavirenz 200 mg to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0,26 to 1,19 % (mean 0,69 %) of the corresponding plasma concentration. This proportion is approximately three-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism:

Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are inactive against HIV-1. CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism.

Elimination:

Efavirenz has a long terminal half-life of 52 to 76 hours after single doses, and 40 to 55 hours after multiple doses. Approximately 14 to 34 % of a radiolabelled dose of efavirenz was recovered in the urine and 16 to 61 % was recovered in faeces, mainly in the form of metabolites.

Special populations:

Hepatic impairment:

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

Renal impairment:

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.

Gender and race:

Pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

Geriatric use:

Pharmacokinetics of efavirenz have not been studied in subjects aged 65 and over to establish whether they respond differently.

Paediatric use:

The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

INDICATIONS:

ADCO EFAVIRENZ, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infected adults, adolescents and children weighing 13 kg and above, and/or 3 years and above.

CONTRAINDICATIONS:

Hypersensitivity to efavirenz or to any of the inactive ingredients of **ADCO EFAVIRENZ** see (**COMPOSITION)**.

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

ADCO EFAVIRENZ should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (e.g. cardiac dysrhythmias, prolonged sedation or respiratory depression).

Pregnancy and lactation (see **PREGNANCY AND LACTATION).**

Children younger than 3 years or weighing less than 13 kg.

WARNINGS AND SPECIAL PRECAUTIONS:

Resistant human immunodeficiency virus (HIV) strains emerge rapidly when **ADCO EFAVIRENZ** is administered as monotherapy, therefore **ADCO EFAVIRENZ** must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. Serious nervous system and psychiatric symptoms have been reported.

When prescribing medicine concomitantly with **ADCO EFAVIRENZ**, medical practitioners should refer to (see **INTERACTIONS**).

If any antiretroviral medicine in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medicine. The antiretroviral medicine should be restarted at the same time upon resolution of the intolerance symptoms. Intermittent monotherapy and sequential reintroduction of antiretroviral agents is not advisable because of the increased potential for selection of drug-resistant mutant virus.

Drug induced liver failure:

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

Patients on **ADCO EFAVIRENZ** 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 **ADCO EFAVIRENZ** or efavirenz containing medicines should be stressed. Patients who discontinued treatment **with ADCO EFAVIRENZ** should be followed up for symptoms/signs of liver failure for up to 12 months.

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

Skin rash:

Mild-to-moderate rash has been reported with **ADCO EFAVIRENZ** use and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. **ADCO EFAVIRENZ** should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with **ADCO EFAVIRENZ** is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of drug resistant virus (see **SIDE EFFECTS**).
Prophylaxis with appropriate antihistamines prior to initiating therapy with **ADCO EFAVIRENZ** in children may be considered.

Nervous system symptoms:

Nervous system symptoms have been reported with **ADCO EFAVIRENZ** use **(**see **SIDE EFFECTS).**

Psychiatric symptoms:

There have been reports of psychosis-like reactions, such as delusions and inappropriate behaviour (including aggressive reactions), predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both **ADCO EFAVIRENZ** -treated and control-treated patients, particularly in patients with a previous

history of depression. Patients should be advised that if they experience these symptoms they should contact their doctor immediately because discontinuation of **ADCO EFAVIRENZ** may be required.

Lipodystrophy and metabolic abnormalities:

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

Immune reconstitution inflammatory syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis:

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

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

Opportunistic infections:

Patients receiving **ADCO EFAVIRENZ** 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 need to be done.

The risk of HIV transmission to others:

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

Special populations:

Because of the extensive cytochrome P450-mediated metabolism of **ADCO EFAVIRENZ** and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering **ADCO EFAVIRENZ** to patients with liver disease.

Liver enzymes:

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

Cholesterol:

Monitoring of cholesterol and triglycerides should be considered in patients treated with **ADCO EFAVIRENZ** (see **SIDE EFFECTS**).

Paediatric use:

ADCO EFAVIRENZ has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg. Therefore, **ADCO EFAVIRENZ** is not recommended in this group (see **CONTRAINDICATIONS**).

Effects on ability to drive and use machines:

ADCO EFAVIRENZ 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 a vehicle or operating machinery.

Contains sugar:

ADCO EFAVIRENZ contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take **ADCO EFAVIRENZ**.

INTERACTIONS:

ADCO EFAVIRENZ is an inducer of CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with **ADCO EFAVIRENZ**.

Indinavir:

When indinavir (800 mg every 8 hours) was given with **ADCO EFAVIRENZ** (200 mg every 24 hours), the indinavir AUC and Cmax were decreased by approximately 31 % and 16 % respectively as a result of enzyme induction. No adjustment of the dose of **ADCO EFAVIRENZ** is necessary when given with indinavir.

Ritonavir:

When **ADCO EFAVIRENZ** 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) was studied in uninfected volunteers the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (for example, dizziness, nausea, paraesthesia and elevated liver enzymes occurred). Monitoring of liver enzymes is recommended when **ADCO EFAVIRENZ** is used in combination with ritonavir.

Saquinavir:

When saquinavir (1 200 mg given 3 times a day, soft gel formulation) was given with **ADCO EFAVIRENZ**, the saquinavir AUC and Cmax were decreased by 62 % and 50 %, respectively. Use of **ADCO EFAVIRENZ** in combination with saquinavir as the sole PI is not recommended.

Rifamycins:

Rifampicin reduced **ADCO EFAVIRENZ** AUC by 26 % and Cmax by 20 % in 12 uninfected volunteers. The dose of **ADCO EFAVIRENZ** must be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with **ADCO EFAVIRENZ**. Rifabutin has not been studied in combination with **ADCO EFAVIRENZ**.

Clarithromycin:

Co-administration of 400 mg of **ADCO EFAVIRENZ** once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and Cmax of clarithromycin decreased 39 % and 26 %, respectively, while the AUC and Cmax of the active clarithromycin hydroxymetabolite were increased 34 % and 49 %, respectively, when used in combination with **ADCO EFAVIRENZ**. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46 % developed rash while receiving **ADCO EFAVIRENZ** and clarithromycin. No dose adjustment of **ADCO EFAVIRENZ** is recommended when given with clarithromycin. Alternatives to clarithromycin may be considered.

Oral contraceptives:

Only the ethinylestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinylestradiol was increased (37 %) after multiple dosing of **ADCO EFAVIRENZ**. No significant changes were observed in Cmax of ethinylestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinylestradiol on efavirenz Cmax or AUC was observed. Because the potential interaction of **ADCO EFAVIRENZ** with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

Methadone:

Co-administration of **ADCO EFAVIRENZ** with methadone, in HIV-infected IV medicine users, 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. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

St John's wort (Hypericum perforatum):

Patients on **ADCO EFAVIRENZ** should not concomitantly use products containing St John's wort (Hypericum perforatum) since it may be expected to result in reduced plasma concentrations of **ADCO EFAVIRENZ**. This effect is due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance.

Cannabinoid test interaction:

ADCO EFAVIRENZ does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received **ADCO EFAVIRENZ.** False positive test results have only been observed with the 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.

PREGNANCY AND LACTATION:

The use of **ADCO EFAVIRENZ** during pregnancy is not recommended, as teratogenicity has been noted. Malformations have been observed in foetuses from **ADCO EFAVIRENZ** (efavirenz)-treated monkeys that received doses, which resulted in plasma medicine concentrations similar to those in humans given 600 mg/day; therefore pregnancy should be avoided in women receiving **ADCO EFAVIRENZ.** 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 prior to initiation of **ADCO EFAVIRENZ (**see **CONTRAINDICATIONS).**

The safety in lactation has not been established. Since animal data suggest that the substance may be passed into breast milk, it is recommended that mothers taking **ADCO EFAVIRENZ do** not breastfeed their infants. It is recommended that HIV-infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

DOSAGE AND DIRECTIONS FOR USE:

Adults:

The recommended dosage of **ADCO EFAVIRENZ** in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily.

ADCO EFAVIRENZ may be taken on an empty stomach, preferably at bedtime.

In order to improve the tolerability of nervous system side effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms (see **SIDE EFFECTS**).

Concomitant antiretroviral therapy:

ADCO EFAVIRENZ must be given in combination with other antiretroviral medicine **(**see **INTERACTIONS).**

Adolescents and children (17 years and younger):

The recommended dose of **ADCO EFAVIRENZ** in combination with a protease inhibitor and/or NRTIs for patients 17 years of age and younger is described in the table below**.**

ADCO EFAVIRENZ should only be administered to children who are able to reliably swallow capsules or tablets.

ADCO EFAVIRENZ may be taken with or without food**.**

ADCO EFAVIRENZ has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg (see **CONTRAINDICATIONS**).

ADCO EFAVIRENZ 600 mg can only be used in adults and children who weigh more than or equal to 40 kg.

Paediatric doses to be administered once daily

Body weight (kg)	**ADCO EFAVIRENZ dose (mg)**
13 to less than 15	200
15 to less than 20	250
20 to less than 25	300
25 to less than 32,5	350
32,5 to less than 40	400
Greater than or equal to 40	600

SIDE EFFECTS:

Immune system disorders:

Less frequent: allergic reaction.

Frequency unknown: immuno-allergic liver injury/failure.

Metabolism and nutrition disorders:

Less frequent: anorexia.

Frequency unknown: redistribution/accumulation of body fat, alcohol intolerance, increased appetite.

Psychiatric disorders:

Less frequent: anxiety, apathy, emotional lability, euphoria, hallucination.

Frequency unknown: aggravated depression.

Nervous system disorders:

Frequent: dizziness, impaired concentration, somnolence, insomnia, headache.

Less frequent: abnormal dreams, hypoesthesia, syncope, agitation, amnesia, ataxia, confusion, impaired coordination, convulsions, migraine headaches, neuralgia, paraesthesia, peripheral neuropathy, speech disorder, tremor, vertigo.

Frequency unknown: abnormal coordination, neuropathy.

Eye disorders:

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, dyspnoea, upper respiratory tract infections.

Gastrointestinal disorders:

Frequent: nausea, vomiting, diarrhoea.

Less frequent: dyspepsia, abdominal pain, taste perversion .

Frequency unknown: gastritis, gastroenteritis, gastroesophageal reflux, constipation, malabsorption.

Hepato-biliary disorders:

Less frequent: hepatitis.

Frequency unknown: hepatic failure.

Skin and subcutaneous tissue disorders:

Frequent: rash, pruritus, increased sweating.

Less frequent: alopecia, eczema, folliculitis, skin exfoliation, urticaria, erythema multiforme, Stevens-Johnson syndrome. .

Frequency unknown: acne, seborrhoea, nail disorders, skin discolouration.

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: flushing, asthenia, malaise.

Frequency unknown: pain, hot flushes, influenza-like symptoms.

Investigations:

Less frequent: raised serum-cholesterol and triglyceride concentrations have been reported, hepatic enzyme increase. Raised liver enzyme values have occurred, particularly in patients with viral hepatitis.

Frequency unknown: weight gain and weight loss.

Description of selected side effects:

***Liver enzymes*:**

Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in 3 % of patients treated with 600 mg of **ADCO EFAVIRENZ**.

Similar elevations were seen in patients treated with control regimens. In 156 patients treated with 600 mg of **ADCO EFAVIRENZ** who were seropositive for Hepatitis B and/or C, 7 % developed AST levels and 8 % developed ALT levels greater than five times the upper limit of the normal range. In 91 patients seropositive for Hepatitis B and/or C, treated with control regimens, 5 % developed AST elevations and 4 % developed ALT elevations to these levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4 % of all patients treated with 600 mg of **ADCO EFAVIRENZ** and in 10 % of patients seropositive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 1,5 to 2 % irrespective of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving **ADCO EFAVIRENZ** may reflect enzyme induction not associated with liver toxicity (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Lipids:

Increases in total cholesterol of 10 to 20 % have been observed in some uninfected volunteers receiving **ADCO EFAVIRENZ**. Increases in non-fasting total cholesterol and HDL of approximately 20 % and 25 %, respectively, were observed in patients treated with efavirenz + ZDV + 3TC and of approximately 40 % and 35 %, in patients treated with **ADCO EFAVIRENZ** + IDV. The effects of **ADCO EFAVIRENZ** on triglycerides and LDL were not well characterised. The clinical significance of these findings is unknown (see **WARNINGS AND SPECIAL PRECAUTIONS**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

Some patients accidentally taking 600 mg of **ADCO EFAVIRENZ** twice daily have reported increased nervous system symptoms and involuntary muscle contractions.

Treatment:

Treatment of overdose with **ADCO 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 **ADCO EFAVIRENZ**. Since **ADCO EFAVIRENZ** is highly protein bound, dialysis is unlikely to significantly remove the medicine from blood.

IDENTIFICATION:

ADCO EFAVIRENZ 50 mg: A hard gelatine capsule, size 4, with opaque white body and opaque white cap containing white granules. Printed, in black, on the cap: "EFV" and body "50".

ADCO EFAVIRENZ 100 mg: A hard gelatine capsule, size 1, with opaque white body and opaque white cap containing white granules. Printed, in black, on the cap: "EFV" and body "100".

ADCO EFAVIRENZ 200 mg: A hard gelatine capsule, size 0, with opaque white body and opaque white cap containing white granules. Printed, in black, on the cap "EFV" and body "200".

ADCO EFAVIRENZ 600 mg: An odourless, white, double convex film coated caplet.

PRESENTATION:

ADCO EFAVIRENZ 50 mg: White, polypropylene or high density polyethylene securitainers in packs of 28's and 30's.

ADCO EFAVIRENZ 100 mg: White, polypropylene securitainers in packs of 30's.

ADCO EFAVIRENZ 200 mg: White, polypropylene securitainers in packs of 84's and 90's.

ADCO EFAVIRENZ 600 mg:

Securitainers:

- 28 and 30 tablets are packed in a white polypropylene securitainer fitted with a low density polyethylene lid.
- 28 and 30 tablets are packed in a white, high density polyethylene securitainer fitted with a white polypropylene child resistant closure, with a heat induction liner.
- A white polypropylene capsule containing silica gel desiccant is included in the container.

Blister packs:

30 tablets are packed in blister strips composed of white opaque PVC/PVDC and aluminium foil. 3 blister strips containing 10 tablets each are packed in an outer cardboard carton.

Amber glass bottles:

30 tablets are packed in a 100 ml amber glass bottle with a silica gel, fitted with a white EXPE screw generic closure.

STORAGE INSTRUCTIONS:

Keep well closed, store in a dry place and at or below 25 °C in the original packaging.

Protect from moisture and light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ADCO EFAVIRENZ 50 mg: 42/20.2.8/0979

ADCO EFAVIRENZ 100 mg: 42/20.2.8/0980

ADCO EFAVIRENZ 200 mg: 42/20.2.8/0981

ADCO EFAVIRENZ 600 mg: 41/20.2.8/0929

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

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand, 1685

Private Bag X69

Bryanston, 2021

www.adcock.com

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Registration date:

ADCO EFAVIRENZ 50 mg: 23 July 2010

ADCO EFAVIRENZ 100 mg: 23 July 2010

ADCO EFAVIRENZ 200 mg: 10 October 2008

ADCO EFAVIRENZ 600 mg: 16 November 2007

Date of revised package insert:

16 May 2017