MODULE 1.3.1.1: Package Insert for

CIPLA EFAVIRENZ 600 (Tablets)

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA EFAVIRENZ 600 (Tablets)

COMPOSITION:

Each tablet contains 600 mg of efavirenz.

Inactive ingredients are lactose monohydrate, magnesium stearate, Opadry yellow (hypromellose, macrogol, titanium dioxide, yellow iron oxide), povidone, pregelatinised starch, and sodium starch glycollate.

Contains sugar (lactose).

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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.

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 – 9,1 μM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

In HIV-infected patients at steady state, mean C_{max}, mean C_{min} and mean AUC were linear with 200 mg, 400 mg and 600 mg daily doses and steady state was reached in 6 to 10 days. In 35 patients receiving efavirenz 600 mg once daily, steady state C_{max} was 12,9 μM, steady state C_{min} was 5,6 μM and AUC was 184 μM•h.

Distribution:

Efavirenz is very highly bound (approximately 99,5 – 99,75 %) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n = 9) who received efavirenz 200 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 threefold 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 and efavirenz inhibits P450 isozymes 2C9, 2C19 and 3A4. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. Multiple doses of 200 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42 % lower) and a shorter terminal half-life of 40 to 55 hours (single doses half-life 52 to 76 hours).

Elimination:

Efavirenz has a long terminal half-life of 52 to 76 hours after single doses, and 40 –

55 hours after multiple doses. Approximately 14 – 34 % of a radio-labelled dose of efavirenz was recovered in the urine and 16 – 61 % was recovered in faeces, mainly in the form of metabolites. Less than 1 % of the dose was excreted in urine as unchanged efavirenz.

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.

Geriatric use:

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

Paediatric use:

In 49 paediatric patients receiving the equivalent of a 600 mg dose of efavirenz (dose adjusted from calculated body size based on weight), steady state C_{max} was 14,2 μM, steady state C_{min} was 5,6 μM, and AUC was 218 μM•h. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

INDICATIONS:

CIPLA EFAVIRENZ 600, in combination with other antiretroviral medicines, is indicated for the treatment of HIV-1 infected adults, adolescents and children weighing 40 kg and above.

CONTRAINDICATIONS:

- **CIPLA EFAVIRENZ 600** is contraindicated in patients with hypersensitivity to efavirenz or any of the ingredients of **CIPLA EFAVIRENZ 600**.
- **CIPLA EFAVIRENZ 600** should not be administered concurrently with astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot derivatives (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine), because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g. cardiac dysrhythmias, prolonged sedation or respiratory depression).
- Pregnancy and lactation (see **"PREGNANCY AND LACTATION"**).
- Children weighing less than 40 kg.
- Severe hepatic impairment (Child-Pugh Class C).
- A history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART).

Herbal preparations containing St. John's wort (*Hypericum perforatum*) must not be used while taking **CIPLA EFAVIRENZ 600** due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see **"INTERACTIONS"**).

WARNINGS AND SPECIAL PRECAUTIONS:

ALERT: Find out about medicines that should NOT be taken with CIPLA EFAVIRENZ 600 (see **"CONTRAINDICATIONS"** and **"SIDE EFFECTS"**).

CIPLA EFAVIRENZ 600 should not be administered concurrently with cisapride, midazolam, triazolam, pimozide, bepridil or ergot derivatives (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine) (see **"CONTRAINDICATIONS"** and **"INTERACTIONS"**).

Concomitant use of *Ginkgo biloba* extracts is not recommended.

Resistant virus emerges rapidly when **CIPLA EFAVIRENZ 600** is administered as monotherapy, therefore, **CIPLA EFAVIRENZ 600** must not be used as a single medicine to treat HIV or added on as a sole medicine to a failing regimen.

When prescribing medicines concomitantly with **CIPLA EFAVIRENZ 600**, medical practitioners should refer to the corresponding manufacturer's product circular.

If **CIPLA EFAVIRENZ 600**, as part of a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medications. The antiretroviral medicines should be restarted at the same time upon resolution of the intolerance symptoms. Intermittent monotherapy and sequential reintroduction of antiretroviral medicines is not advisable because of the increased potential for selection of a resistant mutant virus.

Transmission of infection:

Patients should be advised that current antiretroviral therapy, including **CIPLA EFAVIRENZ 600**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Appropriate contraceptive precautions should continue to be employed.

Skin rash:

Mild-to-moderate rash has been reported with **CIPLA EFAVIRENZ 600** use and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. **CIPLA EFAVIRENZ 600** should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with **CIPLA EFAVIRENZ 600** is discontinued, consideration should also be given to interrupting therapy with other antiretroviral medicines to avoid development of a resistant virus (see **"SIDE EFFECTS"**).

Experience with **CIPLA EFAVIRENZ 600** in patients who discontinued other antiretroviral medicines of the NNRTI class is limited. **CIPLA EFAVIRENZ 600** is not recommended for patients who have had a life-threatening cutaneous reaction (e.g. Stevens-Johnson syndrome) while taking another NNRTI.

Psychiatric symptoms:

Psychiatric adverse reactions have been reported in patients treated with **CIPLA EFAVIRENZ 600**. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions 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 risks of continued therapy outweigh the benefits (see **"SIDE EFFECTS"**).

Nervous system symptoms:

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving **CIPLA EFAVIRENZ 600** daily (see **"SIDE EFFECTS"**). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 – 4 weeks. Patients should be informed that if they do occur, these frequent symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Seizures:

Convulsions have been observed in patients receiving **CIPLA EFAVIRENZ 600**, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicines primarily metabolised by the liver,

such as phenytoin, carbamazepine and phenobarbitone, may require periodic monitoring of plasma levels. Carbamazepine plasma concentrations may be decreased when co-administered with **CIPLA EFAVIRENZ 600** (see **"INTERACTIONS"**). Caution must be taken in any patient with a history of seizures.

Hepatic failure:

There are post-marketing reports of hepatic failure which occurred in patients with no pre-existing hepatic disease or other identifiable risk factors and were characterised by a fulminant course, progressing in some cases to transplantation or death (see **"SIDE EFFECTS"**). Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.

There is evidence that efavirenz is associated with three clinical pathological patterns of medicine induced liver failure in HIV infected patients of which the sub massive necrosis histological pattern seems to be associated with a high morbidity/mortality risk and which 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 **CIPLA EFAVIRENZ 600** 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 **CIPLA EFAVIRENZ 600** or efavirenz containing medicines should be stressed.

Patients who discontinued treatment with **CIPLA EFAVIRENZ 600** should be followed up for symptoms/signs of liver failure for up to 12 months.

CIPLA EFAVIRENZ 600 is not recommended in patients with moderate to severe hepatic impairment because there are insufficient data to determine whether dose adjustments are required (see **"CONTRAINDICATIONS"**).

The safety and efficacy of **CIPLA EFAVIRENZ 600** in patients with both HIV and hepatitis B virus infection have not been established.

Effect of food:

The administration of **CIPLA EFAVIRENZ 600** with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions. It is recommended that **CIPLA EFAVIRENZ 600** be taken on an empty stomach, preferably at bedtime (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Immune reconstitution inflammatory syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination antiretroviral therapy (cART). Typically, such a 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, cryptococcal meningitis and *Pneumocystis jiroveci* (*P.carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

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.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution / accumulation of body fat (lipodystrophy) in HIV patients, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and blood glucose levels (see **"SIDE EFFECTS"**).

Clinical examination should include evaluation for physical signs of fat redistribution. Lipid disorders should be managed as clinically appropriate. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, or 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 **CIPLA EFAVIRENZ 600** 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.

Cholesterol:

Monitoring of cholesterol and triglycerides should be considered in patients treated with **CIPLA EFAVIRENZ 600** (see **"SIDE EFFECTS"**).

Increases in total cholesterol of 10 to 20 % have been observed in uninfected volunteers receiving **CIPLA EFAVIRENZ 600**. Increases in non-fasting total cholesterol and HDL of approximately 20 % and 25 %, respectively, were observed in patients treated with efavirenz + ZDV + lamivudine and of approximately 40 % and 35 %, in patients treated with efavirenz + IDV. The effects of **CIPLA EFAVIRENZ 600** on triglycerides and LDL were not well characterised. The clinical significance of these findings is unknown (see **"SIDE EFFECTS"**).

Special populations:

Liver disease:

CIPLA EFAVIRENZ 600 is contraindicated in patients with severe hepatic impairment (see **"CONTRAINDICATIONS"**) and not recommended in patients with moderate hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering **CIPLA EFAVIRENZ 600** to patients with even mild hepatic impairment. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals.

Liver enzymes:

The safety and efficacy of **CIPLA EFAVIRENZ 600** has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse reactions. Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. In patients with worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with **CIPLA EFAVIRENZ 600** needs to be weighed against the unknown risks of significant liver toxicity (see **"SIDE EFFECTS"**). In such patients, interruption or discontinuation of treatment

must be considered.

In patients treated with other medicines associated with liver toxicity, monitoring of liver enzymes is also recommended. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicines.

Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in patients treated with 600 mg of efavirenz, as in **CIPLA EFAVIRENZ 600**. Similar elevations were seen in patients treated with control regimens. 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 efavirenz, as in **CIPLA EFAVIRENZ 600**, and in 10 % of patients sero-positive for Hepatitis B or C. Isolated elevations of GGT in patients receiving **CIPLA EFAVIRENZ 600** may reflect enzyme induction not associated with liver toxicity (see **"SIDE EFFECTS"**).

Renal insufficiency:

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. There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

Elderly patients:

Insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.

Paediatric use:

CIPLA EFAVIRENZ 600 is not recommended for children weighing less than 40 kg. Rash was reported in 46 % of children treated with **CIPLA EFAVIRENZ 600** and was severe in 5 % of patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with **CIPLA EFAVIRENZ 600**, in children may be considered.

Lactose:

CIPLA EFAVIRENZ 600 contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **CIPLA EFAVIRENZ 600**. Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

Effects on ability to drive and use machines:

CIPLA EFAVIRENZ 600 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.

INTERACTIONS:

Co-administration of **CIPLA EFAVIRENZ 600** with the fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate is not recommended.

CIPLA EFAVIRENZ 600 is an inducer of CYP3A4, CYP2B6 and UGT1A1. Other compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with **CIPLA EFAVIRENZ 600**. **CIPLA EFAVIRENZ 600** is also an inhibitor of CYP3A4 and may therefore initially increase the exposure to CYP3A4 substrates. Caution is warranted for CYP3A4 substrates with narrow therapeutic index (see **"CONTRAINDICATIONS"**).

CIPLA EFAVIRENZ 600 may be an inducer of CYP2C19 and CYP2C9; however, *in vitro* inhibition has also been observed and the net effect of co-administration with substrates of these enzymes is not clear.

CIPLA EFAVIRENZ 600 exposure may be increased when given with medicines (for example, ritonavir) or food (for example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Medicines or herbal preparations (for example *Ginkgo biloba* extracts and St John's wort) which induce these enzymes may give rise to decreased plasma concentrations of **CIPLA EFAVIRENZ 600**. Concomitant use of St. John's wort is contraindicated (see **"CONTRAINDICATIONS"**). Concomitant use of *Ginkgo biloba* extracts is not recommended (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Contraindications of concomitant use:

CIPLA EFAVIRENZ 600 should not be administered concurrently with cisapride, midazolam, triazolam, pimozide, bepridil or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see

"CONTRAINDICATIONS").

Other interactions:

ANTI-INFECTIVES:

HIV antivirals:

Protease inhibitors (PI):

Atazanavir / ritonavir:

Co-administration of **CIPLA EFAVIRENZ 600** with atazanavir/ritonavir (400 mg/100 mg once daily) is not recommended. If the co-administration of atazanavir with an NNRTI is required, an increase in the dose of both atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with **CIPLA EFAVIRENZ 600** could be considered with close clinical monitoring.

Darunavir / ritonavir:

CIPLA EFAVIRENZ 600 in combination with darunavir/ritonavir (800 mg/100 mg once daily) may result in suboptimal darunavir $C_{min.}$ If **CIPLA EFAVIRENZ 600** is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600 mg/100 mg twice daily regimen should be used. This combination should be used with caution.

Fosamprenavir / ritonavir:

No dose adjustment is necessary with fosamprenavir/ritonavir (700 mg/100 mg twice daily).

Fosamprenavir / nelfinavir:

No dose adjustment is necessary with fosamprenavir/nelfinavir.

Fosamprenavir / saquinavir:

Not recommended as the exposure to both PIs is expected to be significantly decreased.

Indinavir:

When indinavir (800 mg every 8 hours) was given with **CIPLA EFAVIRENZ 600** (200 mg every 24 hours), the indinavir AUC and C_{trough} were decreased by approximately 31 % and 16 % respectively, as a result of enzyme induction. See indinavir package insert for dose adjustments.

Indinavir / ritonavir:

When indinavir/ritonavir (800 mg/100 mg twice daily) was given with **CIPLA EFAVIRENZ 600**, the indinavir AUC and C_{min} were decreased by approximately 25 % and 50 % respectively, as a result of enzyme induction. See indinavir/ritonavir package inserts for dose adjustments.

Lopinavir / ritonavir:

With **CIPLA EFAVIRENZ 600**, an increase of the lopinavir/ritonavir soft capsule or oral solution (400 mg/100 mg twice daily) doses by 33 % should be considered (4 capsules/~ 6,5 ml twice daily, instead of 3 capsules/5 ml twice daily). Caution is warranted since this dose adjustment may be insufficient in some patients.

The dose of lopinavir/ritonavir tablets (500 mg/125 mg twice daily) should be increased to 500 mg/125 mg twice daily when co-administered with **CIPLA**

EFAVIRENZ 600 once daily.

Nelfinavir:

No dose adjustment is necessary with nelfinavir.

Ritonavir:

When **CIPLA EFAVIRENZ 600** (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) were studied in infected 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 **CIPLA EFAVIRENZ 600** is used in combination with ritonavir.

Saquinavir:

When saquinavir (1200 mg given 3 times a day, soft capsule formulation) was given with **CIPLA EFAVIRENZ 600**, the saquinavir AUC and C_{max} were decreased by 62 % and 50 % respectively. Use of **CIPLA EFAVIRENZ 600** in combination with saquinavir as the sole protease inhibitor (PI) is not recommended.

Saquinavir / ritonavir:

No data are available to make a dose recommendation. See also ritonavir above. Use of **CIPLA EFAVIRENZ 600** in combination with saquinavir as the sole protease inhibitor is not recommended.

CCR5 antagonist:

Maraviroc:

When maraviroc (100 mg twice daily) was given with **CIPLA EFAVIRENZ 600** (600 mg once daily), the AUC_{12} and C_{max} of maraviroc were decreased by 45 % and 51 %, respectively. Efavirenz concentrations were not measured, no effect is expected.

Integrase strand transfer inhibitor:

Raltegravir:

No dose adjustment is necessary for raltegravir.

NRTIs:

Specific interaction studies have not been performed with **CIPLA EFAVIRENZ 600** and NRTIs other than lamivudine, zidovudine and tenofovir disoproxil fumarate. Clinically significant interactions are not expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways. No dose adjustment is necessary.

NNRTIs:

Since the use of two NNRTIs did not prove to be beneficial in terms of efficacy and safety, co-administration of **CIPLA EFAVIRENZ 600** and another NNRTI is not recommended.

Hepatitis C antivirals:

Boceprevir:

Plasma trough concentrations of boceprevir (800 mg 3 times daily) were decreased

by 44 % when administered with **CIPLA EFAVIRENZ 600** (600 mg once daily). The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.

Telaprevir:

If **CIPLA EFAVIRENZ 600** and telaprevir are co-administered, telaprevir 1,125 mg every 8 hours should be used.

Simeprevir:

Concomitant administration of simeprevir (150 mg daily) with **CIPLA EFAVIRENZ 600** resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of simeprevir. Co-administration of simeprevir with **CIPLA EFAVIRENZ 600** is not recommended.

Antibiotics:

Azithromycin:

No dose adjustment is necessary.

Clarithromycin:

Co-administration of 400 mg of 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 C_{max} of clarithromycin decreased 39 % and 26 %, respectively, while the AUC and C_{max} of the active clarithromycin hydroxymetabolite were increased 34 % and 49 %, respectively, when

used in combination with **CIPLA EFAVIRENZ 600**. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46 % developed rash while receiving **CIPLA EFAVIRENZ 600** and clarithromycin. No dose adjustment of **CIPLA EFAVIRENZ 600** is recommended when given with clarithromycin. Alternatives to clarithromycin may be considered.

Other macrolide antibiotics (e.g. erythromycin):

No data are available to make a dose recommendation.

Antimycobacterials:

Rifamycins:

Rifampicin reduced **CIPLA EFAVIRENZ 600** AUC by 26 % and C_{max} by 20 % in 12 uninfected volunteers. The dose of **CIPLA EFAVIRENZ 600** must be increased to 800 mg/day when taken with rifampicin. **CIPLA EFAVIRENZ 600** is not suitable in these situations.

Rifabutin has not been studied in combination with **CIPLA EFAVIRENZ 600**. The daily dose of rifabutin should be increased by 50 % when administered with **CIPLA EFAVIRENZ 600**. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with **CIPLA EFAVIRENZ 600**.

Antifungals:

Itraconazole:

Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Posaconazole:

Concomitant use of posaconazole and **CIPLA EFAVIRENZ 600** should be avoided unless the benefit to the patient outweighs the risk.

Voriconazole:

When **CIPLA EFAVIRENZ 600** is co-administered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg twice daily and the **CIPLA EFAVIRENZ 600** dose must be reduced by 50 %, i.e. to 300 mg once daily. **CIPLA EFAVIRENZ 600** is not suitable in these situations. When treatment with voriconazole is stopped, the initial dose of **CIPLA EFAVIRENZ 600** should be restored (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Fluconazole:

No dose adjustment is necessary.

Ketoconazole and other imidazole antifungals:

No data are available to make a dose recommendation.

Antimalarials:

Artemether / lumefantrine:

Since decreased concentrations of artemether, dihydroartemisinin or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when **CIPLA EFAVIRENZ 600** and artemether/lumefantrine tablets are co-administered.

Atovaquone and proguanil hydrochloride:

Concomitant administration of atovaquone/proguanil with **CIPLA EFAVIRENZ 600** should be avoided whenever possible.

ACID REDUCING MEDICINES:

Antacids:

Co-administration of **CIPLA EFAVIRENZ 600** with medicines that alter gastric pH would not be expected to affect **CIPLA EFAVIRENZ 600** absorption.

ANTIANXIETY MEDICINES:

Lorazepam:

No dose adjustment is necessary.

ANTICOAGULANTS:

Warfarin:

Dose adjustment of warfarin may be required.

ANTICONVULSANTS:

Carbamazepine:

No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.

Phenytoin, phenobarbitone, and other anticonvulsants that are substrates of CYP450 isoenzymes:

When **CIPLA EFAVIRENZ 600** is co-administered with an anticonvulsant that is a

substrate of CYP450 isoenzymes, periodic monitoring of anticonvulsant levels should be conducted.

Valproic acid:

No dose adjustment is necessary for **CIPLA EFAVIRENZ 600**. Patients should be monitored for seizure control.

Vigabatrin, gabapentin:

No dose adjustment is necessary.

ANTIDEPRESSANTS:

Selective serotonin reuptake inhibitors (SSRIs):

Sertraline:

Sertraline dose increases should be guided by clinical response. No dose adjustment is necessary for **CIPLA EFAVIRENZ 600**.

Paroxetine and fluoxetine:

No dose adjustment is necessary.

NOREPINEPHRINE (NORADRENALINE) AND DOPAMINE REUPTAKE INHIBITOR:

Bupropion:

Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for **CIPLA EFAVIRENZ 600**.

ANTIHISTAMINES:

Cetirizine:

No dose adjustment is necessary.

CARDIOVASCULAR MEDICINES:

Calcium channel blockers:

Diltiazem:

Dose adjustments of diltiazem should be guided by clinical response (refer to the package insert). No dose adjustment is necessary for **CIPLA EFAVIRENZ 600**.

Verapamil, felodipine, nifedipine and nicardipine:

Dose adjustments of calcium channel blockers should be guided by clinical response (refer to the respective package inserts). When **CIPLA EFAVIRENZ 600** is co-administered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme, there is a potential for reduction in the plasma concentrations of the calcium channel blocker.

LIPID LOWERING MEDICINAL PRODUCTS:

HMG Co-A reductase inhibitors:

Atorvastatin, pravastatin and simvastatin:

Co-administration of **CIPLA EFAVIRENZ 600** with atorvastatin, pravastatin or simvastatin did not affect efavirenz AUC or C_{max} values. Cholesterol levels should be periodically monitored. Dose adjustment of atorvastatin, pravastatin or simvastatin

may be required (please refer to the respective package inserts). No dose adjustment is necessary for **CIPLA EFAVIRENZ 600**.

Rosuvastatin:

Rosuvastatin is largely excreted unchanged via the faeces, therefore interaction with **CIPLA EFAVIRENZ 600** is not expected. No dose adjustment is necessary.

HORMONAL CONTRACEPTIVES:

Oral contraceptives:

Only the ethinyloestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinyloestradiol was increased (37 %) after multiple dosing of **CIPLA EFAVIRENZ 600**. No significant changes were observed in C_{max} of ethinyloestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyloestradiol on efavirenz C_{max} or AUC was observed. Because the potential interaction of **CIPLA EFAVIRENZ 600** with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

Depomedroxyprogesterone acetate (DMPA) injection:

Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives.

Etonogestrel implant:

Decreased exposure of etonogestrel may be expected (CYP3A4 induction). There have been occasional post-marketing reports of contraceptive failure with

etonogestrel in **CIPLA EFAVIRENZ 600** exposed patients. A reliable method of barrier contraception must be used in addition to hormonal contraceptives.

IMMUNOSUPPRESSANTS:

Immunosuppressants metabolised by CYP3A4 (e.g. ciclosporin, tacrolimus, sirolimus):

Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with **CIPLA EFAVIRENZ 600**.

OPIOIDS:

Methadone:

Co-administration of **CIPLA EFAVIRENZ 600** with methadone, in HIV-infected IV drug 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.

Buprenorphine / naloxone:

Despite the decrease in buprenorphine exposure, patients do not exhibit withdrawal symptoms. Dose adjustment of buprenorphine or **CIPLA EFAVIRENZ 600** may not be necessary when co-administered.

Cannabinoid test interaction:

CIPLA EFAVIRENZ 600 does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received **CIPLA EFAVIRENZ 600**. 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.

Alcohol or psychoactive medicines:

Patients receiving **CIPLA EFAVIRENZ 600** should be alerted to the potential for additive central nervous system effects when **CIPLA EFAVIRENZ 600** is used concomitantly with alcohol and psychoactive medicines.

PREGNANCY AND LACTATION:

Pregnancy:

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

Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of **CIPLA EFAVIRENZ 600** is recommended.

Women of childbearing potential:

Women of childbearing potential should undergo pregnancy testing prior to initiation of **CIPLA EFAVIRENZ 600** (see **"CONTRAINDICATIONS"**).

Lactation:

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 **CIPLA EFAVIRENZ 600** 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:

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Adults:

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

CIPLA EFAVIRENZ 600 may be taken on an empty stomach, preferably at bedtime. A high fat meal may increase the absorption of **CIPLA EFAVIRENZ 600** and should be avoided.

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:

CIPLA EFAVIRENZ 600 must be given in combination with other antiretroviral medications (see **"INTERACTIONS"**).

Adolescents and children (17 years and under):

CIPLA EFAVIRENZ 600 may be taken on an empty stomach, at bedtime. **CIPLA EFAVIRENZ 600** can only be used in adults and children who weigh greater than, or equal to, 40 kg.

Dose adjustment:

Since **CIPLA EFAVIRENZ 600** is not scored, the tablet should not be halved. This formulation is not suitable for all categories of patients, e.g. children/patients requiring dosage adjustments.

SIDE EFFECTS:

Immune system disorders:

Less frequent:	Hypersensitivity, allergic reaction.
Frequency unknown:	Immuno-allergic liver injury/failure.

Metabolism and nutrition disorders:

Frequent:	Hypertriglyceridaemia.
Less frequent:	Hypercholesterolaemia.
Frequency unknown:	Weight gain, weight loss.

Psychiatric disorders:

Frequent:	Abnormal dreams, anxiety, depression, insomnia.
Less frequent:	Affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis, suicide attempt, suicide ideation, inappropriate behaviour, delusion, neurosis, completed suicide, delirium.
Frequency unknown:	Aggravated depression, emotional lability.

Nervous system disorders:

Frequent:	Cerebellar coordination and balance disturbances, disturbance in attention, dizziness, impaired concentration, somnolence and headache.
Less frequent:	Anorexia, hypoaesthesia, agitation, amnesia, ataxia, abnormal coordination, convulsions, abnormal thinking, tremor, stupor.
Frequency unknown:	Paraesthesia, neuropathy, apathy, increased appetite, confusion, impaired coordination, impotence, decreased libido, increased libido, neuralgia, peripheral neuropathy, speech disorder taste perversion.

Eye disorders:

Less frequent:	Blurred vision.

Frequency unknown: Abnormal vision.

Ear and labyrinth disorders:

Less frequent: Tinnitus, vertigo.

Cardiac disorders:

Frequency unknown: Palpitations, tachycardia.

Vascular disorders:

Less frequent: Flushing.

Frequency unknown: Hot flushes.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Asthma, sinusitis, dyspnoea and upper respiratory tract infections.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea, abdominal pain.

Less frequent: Dyspepsia, pancreatitis.

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

Hepatobiliary disorders:

Frequent: Increased aspartate aminostransferase (AST), increased alanine aminotransferase (ALT),

increased gamma-glutamyltransferase (GGT).

Less frequent: Acute hepatitis, hepatic failure.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus, increased sweating.

Less frequent: Erythema multiforme, Stevens-Johnson syndrome, photo-allergic dermatitis.

Frequency unknown: Acne, alopecia, eczema, folliculitis, seborrhoea, skin exfoliation, urticaria, nail disorders, skin discolouration.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Arthralgia, myalgia, myopathy.

Reproductive system and breast disorders:

Less frequent: Gynaecomastia.

General disorders:

Frequent: Fatigue and pain.

Frequency unknown: Alcohol intolerance, asthenia, influenza-like symptoms, malaise, syncope and redistribution / accumulation of body fat (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Investigations:

Frequency unknown: Raised liver enzyme values (particularly in patients with viral hepatitis), raised serum cholesterol and triglyceride concentrations (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms and involuntary muscle contractions. Treatment of overdose with **CIPLA EFAVIRENZ 600** 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 **CIPLA EFAVIRENZ 600**. Since **CIPLA EFAVIRENZ 600** is highly protein bound, dialysis is unlikely to significantly remove the medicine from blood.

IDENTIFICATION:

Yellow-coloured, capsule-shaped, biconvex tablets debossed with "EFV" on one side and plain on other side.

PRESENTATION:

Available in white plastic bottles containing 28 or 30 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

L.M

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

41/20.2.8/0106

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

CIPLA MEDPRO MANUFACTURING (PTY) LTD

1474 South Coast Road

Mobeni

Durban

4052

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

05 October 2007

Revised: 25 January 2024