SUMMARY OF PRODUCT CHACTERISTICS

1. Name of the Medicinal Product

Efavirenz Tablet 400 mg

2. Qualitative and Quantitative Composition

Each tablet contains:

Efavirenz ..... 400 mg

For Excipients see point 6.1

3. Pharmaceutical Form

Film Coated Tablet

Description - Yellow, capsule shaped, biconvex, film coated tablets, engraved with "C 19" on one side and plain on the other side

4. Clinical Particulars

4.1 Therapeutic indications

Efavirenz in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

4.2 Posology and method of administration

Dosage (adults):

The recommended dosage of Efavirenz is 400 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that Efavirenz be taken on an empty stomach, preferably at bedtime.

Efavirenz must be given in combination with other antiretroviral medications.

Paediatric patients:

It is recommended that Efavirenz be taken on an empty stomach, preferably at bedtime. The following table describes the recommended dose of Efavirenz for pediatric patients 3 years of age or older and weighing between 10 and 40 kg.

Pediatric Dose to be Administered Once Daily

Body Weight (kg)	Efavirenz Dose (mg)
10 to less than 15	200
20 to less than 25	300
32.5 to less than 40	400
at least 40	400

4.3 Contraindications

- **Hypersensitivity:** Efavirenz is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.

4.4 Special warnings and precautions for use

Drug Interactions: Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A or CYP2B6.

Resistance: Efavirenz must not be used as a single agent to treat HIV-1 infection or added on as a sole agent to a failing regimen. Resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

Coadministration with Related Products: Coadministration of Efavirenz with FDC of efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg is not recommended, since efavirenz is one of its active ingredients.

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with Efavirenz. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of Efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Nervous System Symptoms: 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. Dosing at bedtime may improve the tolerability of these nervous system symptoms.

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

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

Rash: Efavirenz can be reinitiated in patients interrupting therapy because of rash. Efavirenz 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. Prophylaxis with appropriate antihistamines before initiating therapy with Efavirenz in pediatric patients should be considered.

Hepatotoxicity: Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. 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 Efavirenz needs to be weighed against the unknown risks of significant liver toxicity.

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 medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels.

Lipid Elevations: Treatment with Efavirenz has resulted in increases in the concentration of total cholesterol and triglycerides. Cholesterol and triglyceride testing should be performed before initiating Efavirenz therapy and at periodic intervals during therapy.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including efavirenz. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits CYP2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs. Drugs that induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Drug interactions with Efavirenz are summarized in the following table:

Concomitant Drug Class: Drug Name	**Effect**	**Clinical Comment**
Antiretroviral agents		
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	**Fosamprenavir (unboosted):** Appropriate doses of the combinations 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 Efavirenz is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when Efavirenz is administered with fosamprenavir plus ritonavir twice daily.

Protease inhibitor: Atazanavir	↓ atazanavir	***Treatment-naive patients:*** When coadministered with Efavirenz, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and Efavirenz 600 mg (once daily on an empty stomach, preferably at bedtime). ***Treatment-experienced patients:*** Coadministration of Efavirenz and atazanavir is not recommended.
Protease inhibitor: Indinavir	↓ indinavir	The optimal dose of indinavir, when given in combination with Efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to Efavirenz. When indinavir at an increased dose (1000 mg every 8 hours) was given with Efavirenz (600 mg once daily), the indinavir AUC and C_{min} were decreased on average by 33-46% and 39-57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir	Lopinavir/ritonavir tablets should not be administered once-daily in combination with Efavirenz. In antiretroviral-naive patients, lopinavir/ritonavir tablets can be used twice daily in combination with Efavirenz with no dose adjustment. A dose increase of lopinavir/ritonavir tablets 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).
Protease inhibitor: Ritonavir	↑ ritonavir ↑ efavirenz	When ritonavir 500 mg q12h was coadministered with Efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when Efavirenz is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir	Should not be used as sole protease inhibitor in combination with Efavirenz.

NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. Efavirenz should not be coadministered with other NNRTIs.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc	
Integrase strand transfer inhibitor: Raltegravir	↓ raltegravir	Efavirenz reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
Hepatitis C antiviral agents		
Protease inhibitor: Boceprevir	↓ boceprevir	Plasma trough concentrations of boceprevir were decreased when boceprevir was coadministered with efavirenz, which may result in loss of therapeutic effect. The combination should be avoided.
Protease inhibitor: Telaprevir	↓ telaprevir ↓ efavirenz	Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by Efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine ↓ efavirenz	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Bupropion	↓ bupropion	The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded.
Sertraline	↓ sertraline	Increases in sertraline dosage should be guided by clinical response.
Antifungals: Voriconazole	↓ voriconazole ↑ efavirenz	Efavirenz and voriconazole must not be coadministered at standard doses. Efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the

		therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of Efavirenz-associated side effects. When voriconazole is coadministered with Efavirenz, voriconazole maintenance dose should be increased to 400 mg every 12 hours and Efavirenz dose should be decreased to 300 mg once daily.
Itraconazole	↓ itraconazole ↓ hydroxyl-itraconazole	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole	Drug interaction studies with Efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Posaconazole	↓ posaconazole	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin ↑ 14-OH metabolite	Plasma concentrations decreased by Efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving Efavirenz and clarithromycin. No dose adjustment of Efavirenz 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 Efavirenz.
Antimycobacterial: Rifabutin	↓ rifabutin	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Calcium channel blockers: Diltiazem	↓ diltiazem ↓ desacetyl diltiazem ↓ N-mono desmethyldiltiazem	Diltiazem dose adjustments should be guided by clinical response. No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (eg, felodipine, nicardipine, nifedipine,	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A. The potential

verapamil)		exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response.
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin[a] ↓ pravastatin[a] ↓ simvastatin[a]	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased.
Hormonal contraceptives: Oral Ethinyl estradiol / Norgestimate	↓ active metabolites of norgestimate	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
Implant Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓ immunosuppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction. These immunosuppressants are not anticipated to affect exposure of efavirenz. 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 efavirenz.
Narcotic analgesic: Methadone	↓ methadone	Coadministration in HIV-infected individuals with a history of injection drug 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.

4.6 Pregnancy and Lactation

Pregnancy:

Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving Efavirenz. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of Efavirenz. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

Lactation:

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, mothers should be instructed not to breast-feed if they are receiving Efavirenz.

4.7 Effects on ability to drive and use machines

Efavirenz may cause dizziness, impaired concentration, and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

The adverse reactions observed in patients treated with Efavirenz are:

Body as a Whole: Fatigue, Pain

Central and Peripheral Nervous System: Dizziness, Headache, Insomnia, Concentration impaired, Abnormal dreams, Somnolence, Anorexia, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking and depersonalization

Gastrointestinal: Nausea, Vomiting, Diarrhea, Dyspepsia, Abdominal pain

Psychiatric: Anxiety, Depression and Nervousness

Skin & Appendages: Rash, Pruritus, erythema, diffuse maculopapular rash, dry desquamation, vesiculation, moist desquamation, ulceration, erythema multiforme, stevens-johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis.

4.9 Overdose

Some patients accidentally taking 400 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Treatment of overdose with Efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with Efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group **:** Non-nucleoside reverse transcriptase inhibitors

ATC Code for Efivirenz **:** J05AG03

Mechanism of Action:

Efavirenz (EFV) is an NNRTI of HIV-1. EFV activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ are not inhibited by EFV.

Antiviral Activity in Cell Culture:

The concentration of EFV inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90-95% (EC90-95) ranged from 1.7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. EFV demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. EFV

demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV]), PIs (amprenavir, indinavir [IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. EFV was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Resistance:

In cell culture: In cell culture, HIV-1 isolates with reduced susceptibility to EFV (> 380-fold increase in EC90 value) emerged rapidly in the presence of drug. Genotypic characterization of these viruses identified single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in RT.

Cross-Resistance: Cross-resistance among NNRTIs has been observed. Clinical isolates previously characterized as EFV-resistant were also phenotypically resistant in cell culture to DLV and NVP compared to baseline. DLV- and/or NVP-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 EFV in cell culture. Greater than 90% of NRTI-resistant clinical isolates tested in cell culture retained susceptibility to EFV.

5.2 Pharmacokinetic properties

Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. Studies in humans and in vitro studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The in vitro studies suggest that CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in the induction of

its own metabolism. Multiple doses of 200-400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half-life of 40-55 hours (single dose half-life 52-76 hours).

5.3 Preclinical safety data

Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. There was no NOAEL in females established for this study because tumor findings occurred at all doses. AUC at the NOAEL (150 mg/kg) in the males was approximately 0.9 times that in humans at the recommended clinical dose. In the rat study, no increases in tumor incidence were observed at doses up to 100 mg/kg/day, for which AUCs were 0.1 (males) or 0.2 (females) times those in humans at the recommended clinical dose.

Efavirenz tested negative in a battery of *in vitro* and *in vivo* genotoxicity assays. These included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an in vivo mouse bone marrow micronucleus assay.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. The AUCs at the NOAEL values in male (200 mg/kg) and female (100 mg/kg) rats were approximately ≤ 0.15 times that in humans at the recommended clinical dose.

SUMMARY OF PRODUCT CHARACTERISTIC

6. Pharmaceutical Particulars

6.1 List of Excipients

Core tablet: Croscarmellose sodium, Hydroxypropyl cellulose, Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose and Sodium lauryl sulphate.

Film coating (Opadry 03B52055 Yellow): Hypromellose, Titanium dioxide, Polyethylene glycol and Yellow iron oxide non-irradiated

6.2 Incompatibilities

None

6.3 Shelf life

24 months from the manufacturing date.

Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

"Do not store above 30°C, protect from light"

6.5 Nature and contents of container

30 Tablets packed in 60 cc white, round HDPE HW container with 33 mm child resistance polypropylene closure with HS 123 white printed liner and finally induction sealed. Individual container is to be further packed in a box along with the pack insert.

6.6 Special Precaution for disposal

None.

7. Supplier

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8. Market authorization Number

04877/3839/NMR/2017

9. Date of authorization/ last renewal

Dec 31, 2019

10. Date of Revision of the Text:
July 2016

References:

1. Pack Insert of Sustiva (Efavirenz) Tablet, 600mg, available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=32d6371e-ba56-4294-b732-6d43627c5c47.

2. SPC of Sustiva (Efavirenz) Tablet, 600mg available at https://www.medicines.org.uk/emc/medicine/31688.
3. http://www.cipla.com/uploads/mediakit/1448864830_Press%20Release%20-Launch%20of%20low-dose%20Efavirenz.pdf