PUBLIC ASSESSMENT REPORT

Efavirenz Capsules 50 mg, 100 mg, and 200 mg

International Nonproprietary name (INN): **Efavirenz**

Abstract

Efavirenz Capsules 50 mg, 100 mg, and 200 mg, manufactured by Aurobindo Pharma Ltd., Hyderabad 500 072, India, was the subject of an abbreviated new drug application (ANDA) submitted to the U. S. Food and Drug Administration (USFDA) pursuant to section 505(j) of the U. S. Federal Food, Drug, and Cosmetic Act.

This ANDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR). Based upon the information presented to date the USFDA concluded that Efavirenz Capsules 50 mg, 100 mg, and 200 mg are safe and effective for use as recommended in the submitted labeling. The USFDA was unable to grant final approval to this ANDA at the time of review due to existing patent protection. Therefore, the ANDA was **tentatively approved** on December 19, 2006. This determination is based upon information available to the agency (i.e., information in the ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product.

Efavirenz Capsules 50 mg, 100 mg, and 200 mg, on the basis of USFDA **tentative approval**, was placed on the WHO Prequalification Programme list of manufacturers and suppliers whose HIV-related products have been found acceptable, in principle, for procurement by UN Agencies (Prequalification Programme: Priority Essential Medicines, 63rd Edition, 1 February 2008).

Products listed on the WHO Prequalification list with the note "USFDA" have been added to the list based on the scientific assessment and inspections conducted by the USFDA. A product listed as USFDA **tentatively approved** indicates that although existing patents and/or other marketing exclusivity prevent marketing of the product in the USA, the product meets all of USFDA's safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

Efavirenz is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC), Part 4 of this Public Assessment Report.

The active pharmaceutical ingredient (API) of Efavirenz Capsules 50 mg, 100 mg, and 200 mg is the non-nucleoside reverse transcriptase inhibitor efavirenz, a well established and documented active substance for the treatment of HIV/AIDS in combination with other products.

The API has been investigated in combination therapy in several clinical trials, in both treatment-naïve and treatment-experienced patients. These studies have demonstrated significant decreases in viral load as well as increases in CD4 cell counts. Long-term results after 3 years of combination therapy with efavirenz suggest durability of virological and immunological responses.

The most frequent adverse reactions observed during treatment were nervous system disorders, such as headache, confusion, insomnia, dizziness and abnormal dreaming, skin rash, fatigue, increases in blood lipids and elevations of liver enzymes.

The most notable unwanted effects are skin rash and nervous system symptoms that include dizziness, insomnia, somnolence (drowsiness), impaired concentration, abnormal dreaming, depression, psychosis, suicide ideation and/or attempt. Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse events.

The risk/benefit profile of Efavirenz Capsules 50 mg, 100 mg, and 200 mg showed acceptable safety and adequate antiretroviral activity. Efavirenz in any form or strength is not recommended for use as monotherapy because of rapid emergence of resistance. Efavirenz must not be used in patients with clinically significant hypersensitivity to efavirenz or to any of the components contained in the formulation.

All Accepted Presentations

Status	USFDA Tentative Approval 12/19/2006
INN	Efavirenz
Strength	50 mg, 100 mg, 200 mg
Form	Capsules
Route of administration	Oral
Packaging	Bottle, unit-dose packaging
Package size	Bottles of 30 (50 mg, 100 mg, and 200 mg) Bottles of 90 (200 mg) 3 x 10 unit-dose (50 mg, 100 mg, and 200 mg) 9 x 10 unit-dose (200 mg)

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Efavirenz Capsules 50 mg, 100 mg, and 200 mg

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. WHAT EFAVIRENZ CAPSULES ARE AND WHAT THEY ARE USED FOR

Efavirenz belongs to a group of antiviral medicines, also known as antiretrovirals, called "non-nucleoside reverse transcriptase inhibitors," or "NNRTIs." Efavirenz is used in combination with other antiretroviral medicines for the treatment of HIV-1 (Human Immunodeficiency Virus type 1) infection. Efavirenz reduces the amount of HIV virus in your body and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cell that plays an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Efavirenz varies between patients. Your doctor or health care provider will be monitoring the effectiveness of your treatment.

Efavirenz may improve your condition but is not a cure for HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with efavirenz has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

During your treatment, other infections linked to your weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. BEFORE YOU TAKE EFAVIRENZ CAPSULES

Do not take Efavirenz Capsules if:
- you are allergic (hypersensitive) to efavirenz or any other ingredients of Efavirenz Capsules (see Part 6, What Efavirenz Capsules contain).

Take special care with Efavirenz Capsules
Before using this medicine, you should tell your doctor or health care provider:
- if you suffer from liver disease (such as hepatitis)
- about past or present medical problems including allergies, seizures, mental illness, or substance or alcohol abuse

A mild-to-moderate skin rash commonly develops in the first two weeks after starting efavirenz. This rash usually resolves within 4 weeks of the start of treatment. In case of a progression to a severe rash you must tell your doctor or health care provider immediately and efavirenz capsules may have to be discontinued.

Nervous system side effects are very common after starting treatment with efavirenz, usually occurring in the first week of treatment. These side effects may include dizziness, confusion, insomnia, somnolence, impaired concentration, and/or abnormal dreaming. Other side effects are amnesia, hallucinations, euphoria, or psychosis. These side effects usually resolve within four weeks of starting treatment.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor or health care provider immediately.

You must take your prescribed dose of efavirenz every day. Efavirenz helps to control your condition is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. You should maintain regular contact with your doctor or health care provider. Do not stop taking your medicine without first talking to your doctor or health care provider.

Taking other medicines
Tell your doctor, health care provider, or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription such as vitamins or nutritional supplements. These may affect the action of Efavirenz Capsules, or Efavirenz Capsules may affect their action.

The following medicines may cause serious and life-threatening side effects when taken with efavirenz. You should not take any of these medicines while taking Efavirenz Capsules:

- Hismanal® (astemizole)*
- Vascor® (bepridil)
- Propulsid® (cisapride)*
- Versed® (midazolam)
- Orap® (pimozide)
- Halcion® (triazolam)
- Ergot medications (for example, Wigraine® and Cafergot®)

* These drugs are not marketed in the U.S., Canada, or Europe but are available in many countries.

Vfend® (voriconazole) should not be taken with Efavirenz Capsules as it may lose its effect or may increase the chance of having side effects from efavirenz. Some doses of voriconazole can be taken at the same time as a lower dose of efavirenz, but you must check with your doctor first.

Herbal preparations containing St John's wort (*Hypericum perforatum*) must ***not*** be taken with Efavirenz Capsules.

The following medicines may need to be replaced with another medicine when taken with Efavirenz Tablets:

- Fortovase®, Invirase® (saquinavir)
- Biaxin® (clarithromycin)
- Carbatrol®, Tegretol® (carbamazepine)
- Sporanox® (itraconazole)

The following medicines may require a change in the dose of either efavirenz or the other medicine:

- Calcium channel blockers such as Cardizem® or Tiazac® (diltiazem), Covera HS® or Isoptin SR® (verapamil), and others.
- The cholesterol-lowering medicines Lipitor® (atorvastatin), PRAVACHOL® (pravastatin), and Zocor® (simvastatin)
- Crixivan® (indinavir)
- Kaletra® (lopinavir/ritonavir)
- Methadone
- Mycobutin® (rifabutin)
- Reyataz® (atazanavir sulfate). If you are taking Efavirenz Tablets and Reyataz, you should also be taking Norvir® (ritonavir).
- Rifadin® (rifampin) or the rifampin-containing medicines Rifamate® and Rifater®.
- Zoloft® (sertraline)

If you are being treated with methadone when you start taking efavirenz, your doctor or health care provider may have to adjust your dose of methadone.

Tell your doctor about all medicines that you take, even non-prescription ("over the counter") medicines, vitamins, or food supplements.

Contraception (Birth Control)
For women taking efavirenz, barrier contraception (for example, condoms) should always be used in combination with other contraceptive methods.

Taking Efavirenz with food and drink
Efavirenz should be taken on an empty stomach or with a low-fat meal.

Pregnancy
Tell your doctor immediately if you are currently pregnant or intend to become pregnant. If you are pregnant, you should take Efavirenz Capsules only if you and your doctor decide they are clearly needed. Malformations have been seen in fetuses from animals and in newborns of women treated with Efavirenz. Therefore, pregnancy should be avoided in women receiving Efavirenz Capsules. If you are a woman receiving Efavirenz Capsules a reliable form of barrier contraception (for example, a condom) should always be used, along with other methods of contraception including oral ("the pill") or other hormonal contraceptives (for example, implant or injection).

Breastfeeding
You should ***not*** breastfeed your baby if you are taking Efavirenz Capsules.

Driving and using machines
Dizziness, poor concentration, and drowsiness have been reported during treatment with efavirenz. If you experience these symptoms you should avoid potentially hazardous tasks such as driving or operating machinery.

3. HOW TO TAKE EFAVIRENZ CAPSULES

Always take Efavirenz Capsules 50 mg, 100 mg, or 200 mg exactly as your doctor or health care provider has told you. You should check with your doctor, health care provider, or pharmacist if you are not sure how to take them.

The usual daily dose for adults and adolescents weighing 40 kg (88 lbs) or more is 600 mg, given once daily. The dose of Efavirenz Capsules will be adjusted to lower strengths if an individual weighs less than 40 kg (88 lbs) or is a child. Always take Efavirenz Capsules exactly as your doctor or health care provider tells you to.

Efavirenz Capsules should be taken on an empty stomach or with a low-fat meal, for example, in the evening before going to bed.

Efavirenz Capsules will always be taken in combination with other antiretroviral medication. Always follow the instructions within the supplied package leaflet.

If you take more Efavirenz Capsules than you should
If you take too many Efavirenz capsules, consult your doctor or go to your local clinic or hospital.

If you forget to take Efavirenz Capsules
Try not to miss a dose. If you do, take the next dose as soon as possible. If close to the time of your next dose, simply take that dose as scheduled. Do NOT double any dose because you missed a previous dose.

If you stop taking Efavirenz Capsules
Do not stop taking Efavirenz Capsules unless you experience serious side effects or your doctor tells you to stop. This is very important because the amount of HIV virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat. If you have any further questions on the use of this product, ask your doctor, health care provider, or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Efavirenz Capsules can cause side effects, although not everybody who takes them will experience side effects.

The most frequently reported adverse reactions associated with efavirenz in combination with other anti-HIV medicines includes rash, dizziness, nausea, headache, and fatigue.

You should consult your doctor if you have a rash, since some rashes may be serious. However, most cases of rash disappear without any change to your treatment with Efavirenz Capsules. Rash was more common in children than in adults treated with efavirenz.

Very commonly reported side effects (greater than 1 in every 10 patients treated): rash, dizziness, confusion, insomnia (inability to sleep), somnolence (sleepiness), poor concentration, odd dreams or nightmares, headache, fatigue, and increases in fats in the blood (triglycerides and cholesterol).

Commonly reported side effects *(greater than 1 in every 100 patients treated)*: disturbed liver function (detected by a blood test that shows elevation of chemicals made by the liver), anxiety and/or depression, and excessive development of the breast in the male (gynecomastia).

Uncommonly reported *(between 1 in 100 and 1 in 1,000 patients treated)*: psychosis (a mental state with abnormal thinking and perception). The likelihood of this side effect is increased in those with a history of psychiatric disease.

Combination antiretroviral therapy may cause a condition called lactic acidosis, a build-up of an acid (lactic acid) in the body that can cause dehydration and coma. Lactic acidosis has been reported on rare occasions in patients taking NRTIs. Deep, rapid breathing, drowsiness, and symptoms such as nausea, vomiting, and stomach pain, may all be indicators of lactic acidosis.

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms, and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ("buffalo hump"). The cause and long-term health effects of these conditions are not known at this time.

Combination antiretroviral therapy may also cause elevations of sugar in the blood, hyperlipemia (increased fats in the blood), and resistance to insulin.

If you experience any of these side effects, or if you experience any side effects not listed in this leaflet, tell your doctor, health care provider, or pharmacist immediately.

5. HOW TO STORE EFAVIRENZ CAPSULES

- Store at 20° to 25°C (68° to 77°F) with occasional periods permitted between 15° and 30°C (59° to 86°F).
- Keep out of the reach and sight of children.
- Do not use Efavirenz Capsules after the expiration (expiry) date which is stated on the label and carton. The expiration [expiry] date refers to the last day of that month.
- Do not use Efavirenz Capsules if you notice any visible signs of deterioration.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Efavirenz Capsules contain

The active ingredient is efavirenz. The inactive ingredients are sodium starch glycolate, sodium lauryl sulfate, lactose monohydrate, and magnesium stearate. The capsule shell contains silicon dioxide, sodium lauryl sulfate, gelatin, and yellow iron oxide. The capsule shell for the 50 mg and

100 mg products also contains titanium dioxide. The capsules are printed with edible ink containing black iron oxide and shellac.

What Efavirenz Capsules 50 mg, 100 mg, and 200 mg look like and contents of the packages

Efavirenz Capsules 50 mg are yellow and white hard gelatin capsules imprinted with 'D' on the yellow cap and '72' on the white portion with black edible ink.

Efavirenz Capsules 100 mg are white hard gelatin capsules imprinted with 'D' on the white cap and '71' on the white body with black edible ink.

Efavirenz capsules 200 mg are yellow hard gelatin capsules imprinted with 'D' on the yellow cap and '36' on the yellow body with black edible ink.

The capsules are filled with white to off-white colored powder.

Efavirenz Capsules are packaged in bottles of 30 (50 mg, 100 mg, and 200 mg), bottles of 90 (200 mg), and in unit-dose packages: 3 x 10 unit-dose (50 mg, 100 mg, and 200 mg) and 9 x 10 unit-dose (200 mg)

For further information about this medicinal product, please contact the supplier: Aurobindo Pharma Ltd., Hyderabad 500 072, India.

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz Capsules 50 mg, 100 mg, and 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mg capsule contains 50 mg of efavirenz.
Each 100 mg capsule contains 100 mg of efavirenz.
Each 200 mg capsule contains 200 mg of efavirenz.
For excipients see 6.1

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efavirenz is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

4.2 Posology and method of administration

Oral use.

Therapy should be prescribed by a physician experienced in the diagnosis and management of HIV-1 infection.

Adults and adolescents over 40 kg: the recommended dosage of efavirenz in any form is 600 mg orally, once daily.

Adolescents and children (weighing ≥13 kg): the recommended doses are described in the table.

Table: Pediatric dose to be administered once daily*

Body Weight (kg)	Efavirenz dose (mg)
13 to <15	200
15 to <20	250
20 to <25	300
25 to <32.5	350
32.5 to <40	400
≥40	600

**In patients whose body weight is less than 40 kg another formulation should be used, e.g., a tablet or capsule containing less efavirenz.*

Efavirenz should be taken on an empty stomach or with a low-fat meal.

Liver Disease
No dose adjustment is necessary for mild to moderate liver impairment, but discontinuation may be necessary for severe liver impairment.

Renal Impairment
No dose modification is necessary.

4.3 Contraindications

Efavirenz is contraindicated in patients with clinically significant hypersensitivity to efavirenz or to any of the components contained in the formulation.

4.4 Special warnings and special precautions for use

Efavirenz should not be used as part of a triple combination regimen consisting of efavirenz, didanosine, and tenofovir because of inferior efficacy compared to other combination regimens.

Rash
A mild-to-moderate rash commonly (15-30%) develops within two weeks after starting efavirenz and does not require discontinuation. The rash usually resolves within two weeks. Severe rash (1-2%) or erythema / Stevens-Johnson syndrome (< 0.1%) requires immediate discontinuation. Patients who discontinued treatment with other NNRTIs due to rash may be at higher risk of developing rash during treatment with efavirenz.

Central nervous system
Central nervous system side effects are very common (~50%) after starting efavirenz. These symptoms typically occur within the first week of treatment and usually resolve within 4 weeks of treatment. Symptoms include confusion, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Other side effects include amnesia, hallucinations, euphoria and psychosis.

There is a potential additive effect with alcohol and other psychoactive drugs.

Liver toxicity
Increased transaminase levels may occur months after starting efavirenz and may be more frequent in those with HCV co-infection. Discontinuation is recommended if hepatoxicity is symptomatic (infrequent), caused by hypersensitivity, or if the transaminase levels are > 10 times the upper limit of normal.

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz is an inducer of the hepatic enzyme CYP3A4 and an inhibitor of some CYP isozymes including CYP4A; therefore, it is possible that co-administration of efavirenz with medicinal products (for example, astemizole, terfenadine, cisapride, midazolam, triazolam, ergot derivatives and St. John's wort) or food (for example, grapefruit juice) which affect CYP3A4 activity may result in an alteration in the plasma concentration of either agent. (Note: astemizole, terfenadine, and cisapride are no longer marketed in the U.S., Canada, or Europe, but are available in many countries, including in many PEPFAR focus countries.)

Efavirenz decreases plasma concentrations of methadone. Methadone-maintained patients beginning efavirenz therapy should be assessed for evidence of withdrawal and methadone dose should be adjusted accordingly.

Rifampicin may significantly decrease levels of efavirenz. Rifampicin levels are unaffected.

Efavirenz decreases serum levels of atorvastatin, pravastatin and simvastatin.

Efavirenz decreases serum levels of clarithromycin; the risk of rash is significantly increased.

Efavirenz increases levels of ethinyl estradiol. Barrier contraception should always be used in combination with other contraceptive methods.

Efavirenz significantly decreases levels of amprenavir, atazanavir, indinavir, lopinavir, and saquinavir but increases levels of nelfinavir and ritonavir. Therefore, if efavirenz is given with either of these drugs, either dosage adjustments or, alternatively, ritonavir boosting may be necessary. Efavirenz does not alter the levels of fosamprenavir or tipranavir. Ritonavir significantly increases levels of efavirenz.

Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV infected volunteers receiving efavirenz when the Microgenics CEDIA DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry. Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THC assay, Cannabinoid Enzyme Immunoassay (Diagnostic Reagents, Inc.), and the AxSYM Cannabinoid Assay), only the Microgenics CEDIA assay showed false-positive results. The other two assays provided true-negative results. The effects of efavirenz on cannabinoid screening tests other than these three are unknown. The manufacturers of cannabinoid assays should be contacted for additional information regarding the use of their assays with patients receiving efavirenz.

4.6 Pregnanacy and lactation

Efavirenz is assigned USFDA Pregnancy Category D status ("positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"). Cases of neural tube defects in infants born to women with first trimester exposure have been reported. Efavirenz is generally contraindicated in women willing to become pregnant or in case of a positive pregnancy test.

The U.S. 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 central nervous system side effects such as 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 following adverse events have been reported in controlled clinical trials and case series during treatment of HIV-1 infection with efavirenz.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class, and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100 / <1/10), uncommon (>1/1000 / <1/100), rare (>1/10,000 / <1/1000), and very rare (<1/10,000).

Metabolic and nutritional disorders
Very common: increases in fasting triglycerides, total cholesterol, high- and low-density lipoprotein cholesterol
Common: gynecomastia

Nervous system disorders
Very common: confusion, dizziness, insomnia, somnolence, impaired concentration, abnormal dreaming, headache
Common: anxiety and/or depression
Uncommon: psychosis (increased likelihood in those with history of psychiatric disease)

Hepatobiliary disorders
Common: elevation of liver enzymes

Skin and subcutaneous tissue disorders
Very common: rash

General disorders
Very common: fatigue

4.9 Overdose

Some patients who accidentally took as much as 600 mg of efavirenz twice daily reported increased nervous system symptoms. One patient experienced involuntary muscle contractions. Treatment of efavirenz overdose 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 efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of efavirenz from blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-nucleoside reverse transcriptase inhibitor (NNRTI)
ATC Code: J05AG03

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a conformational change that causes a disruption of the enzyme's catalytic site.

The activity of efavirenz does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by efavirenz.

Clinical efficacy and drug resistance
Efavirenz has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs. These studies have demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with nucleoside analogue(s) and/or a PI. In recent studies by intention-to-treat analysis > 70% of subjects have achieved plasma HIV RNA < 50 copies/ml after 48 weeks of combination treatment that included efavirenz with other antiretroviral drugs.

HIV-1 resistance to efavirenz involves the development of mutations in the reverse transcriptase gene at positions 100, 103, 106, 108, 181, 188 and 190. The K103N or Y188L mutation alone prevents the clinical utility of efavirenz. The V106M mutation is more common in HIV-1 subtype C than subtype B.

Rapid emergence of resistance to NNRTIs, including efavirenz, is likely to occur in case of virological failure.

Patients infected with known efavirenz-resistant HIV or patients who have previously experienced virological failure on an efavirenz- or nevirapine-containing regimen may not respond sufficiently to further treatment with a combination regimen containing efavirenz or nevirapine.

5.2 Pharmacokinetic properties

Absorption and Bioavailability: Bioavailability is 40% to 45% without food. Fat-containing meals increase absorption significantly.

Peak efavirenz plasma concentrations of 1.6 - 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. Time to peak plasma concentrations (3 - 5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6 - 7 days.

In HIV infected patients at steady state, mean Cmax, mean Cmin, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady state Cmax was 12.9 ± 3.7 μM (29%) mean ± S.D. (% C.V.), steady state Cmin was 5.6 ± 3.2 μM (57%), and AUC was 184 ± 73 μM·h (40%).

Distribution: Efavirenz is 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 3-fold higher than the nonprotein-bound (free) fraction of efavirenz in plasma.

Metabolism / Elimination: 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. *In vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. *In-vitro* studies of 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. In uninfected volunteers, multiple doses of 200-400 mg daily 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).

Efavirenz has a relatively long terminal half-life of 52-76 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 less than 1% of the dose was excreted in urine as unchanged efavirenz.

5.3 Preclinical safety data

Preclinical data revealed no specific hazard for humans other than those observed in clinical studies based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In reproductive toxicology studies, malformations were observed in 3 of 20 fetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate, sodium lauryl sulfate, lactose monohydrate, and magnesium stearate, with a capsule shell containing silicon dioxide, sodium lauryl sulfate, gelatin, and yellow iron oxide. The capsule shell for the 50 mg and 100 mg products also contains titanium dioxide. The capsules are printed with edible ink containing black iron oxide and shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

6.5 Nature and contents of container

Efavirenz Capsules 50 mg are yellow/white size '4' hard gelatin capsules imprinted with 'D' on yellow cap and '72' on white body with black edible ink filled with white to offwhite colored powder.

Efavirenz Capsules 100 mg are white/white size '2' hard gelatin capsules imprinted with 'D' on white cap and '71' on white body with black edible ink filled with white to offwhite colored powder.

Efavirenz capsules 200 mg are yellow/yellow size '0EL' hard gelatin capsules imprinted with 'D' on yellow cap and '36' on yellow body with black edible ink filled with white to off-white colored powder.

Packaging: bottles of 30 (50 mg, 100 mg, and 200 mg), bottles of 90 (200 mg), 3 x 10 unit-dose capsules (50 mg, 100 mg, and 200 mg), 9 x 10 unit-dose capsules (200 mg).

6.6 Instructions for use and handling and disposal

No special requirements.

7. Supplier

Aurobindo Pharma Ltd., Hyderabad 500 072, India

8. DATE OF USFDA TENTATIVE APPROVAL

December 19, 2006

LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Efavirenz Capsules 50 mg, Efavirenz Capsules 100 mg, Efavirenz Capsules 200 mg

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz Capsules

2. STATEMENT OF ACTIVE SUBSTANCE

Capsules contain either 50 mg, 100 mg, or 200 mg of efavirenz

3. LIST OF EXCIPIENTS

Sodium starch glycolate, sodium lauryl sulfate, lactose monohydrate, and magnesium stearate, silicon dioxide, sodium lauryl sulfate, gelatin, yellow iron oxide, titanium dioxide, black iron oxide, shellac

4. PHARMACEUTICAL FORM AND CONTENTS

Efavirenz Capsules 50 mg: Yellow/White size ‘4’ hard gelatin capsules imprinted with ‘D’ on yellow cap and ‘72’ on white body with black edible ink filled with white to offwhite colored powder.

Efavirenz Capsules 100 mg: White/White size ‘2’ hard gelatin capsules imprinted with ‘D’ on white cap and ‘71’ on white body with black edible ink filled with white to offwhite colored powder.

Efavirenz capsules 200 mg: Yellow/Yellow size ‘0EL’ hard gelatin capsules imprinted with ‘D’ on yellow cap and ‘36’ on yellow body with black edible ink filled with white to off-white colored powder.

Supplied in bottles of 30 (50 mg, 100 mg, and 200 mg), bottles of 90 (200 mg), 3 x 10 unit-dose capsules (50 mg, 100 mg, and 200 mg), 9 x 10 unit-dose capsules (200 mg)

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

8. EXPIRATION (EXPIRY) DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE SUPPLIER

Aurobindo Pharma Ltd., Hyderabad 500 072, India

12. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> <BN> {number}

13. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

14. INSTRUCTIONS ON USE

SCIENTIFIC DISCUSSION

DISCUSSION

Name of the Finished Pharmaceutical Products:	Efavirenz 50 mg capsules Efavirenz 100 mg capsules Efavirenz 200 mg capsules
Supplier:	Aurobindo Pharmaceuticals, Ltd.
Active Pharmaceutical Ingredient (API):	Efavirenz
International Non-proprietary Name:	Efavirenz
Pharmaco-therapeutic group (ATC Code):	Efavirenz J05AG03
Therapeutic indication:	Indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

1. Introduction

Efavirenz Capsules 50 mg, 100 mg, or 200 mg are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Efavirenz is not indicated for use in patients with clinically significant hypersensitivity to efavirenz or any of the components contained in the formulation.

It is recommended that therapy be initiated only on the advice of a physician experienced in the diagnosis and management of HIV-1 infection.

2. Assessment of Quality

Introduction
The assessment was conducted by the USFDA as an abbreviated new drug application (ANDA) reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR).

Composition
Efavirenz Capsules 50 mg are capsules containing 50 mg efavirenz as the active pharmaceutical ingredient (API).
Efavirenz Capsules 100 mg are capsules containing 100 mg efavirenz as the active pharmaceutical ingredient (API).
Efavirenz Capsules 200 mg are capsules containing 200 mg efavirenz as the active pharmaceutical ingredient (API).
Efavirenz Capsules 50 mg, 100 mg, and 200 mg are generic versions of Sustiva® 50 mg, 100 mg, and 200 mg capsules.

Control of active pharmaceutical ingredient (API)

Efavirenz Capsules are controlled as per specifications in the application and cGMPs, and are consistent with general USP requirements and product- and process-specific needs and information.

Control testing of the finished medicinal product
The release and shelf-life specifications are in line with requirements of major internationally used pharmacopoeias and guidelines for capsules. The test methods have been adequately validated. Critical process variables were optimized during the pharmaceutical R&D stage. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Stability
Stability studies have been conducted and results show that the products conform with the proposed end of shelf life specification including description, disintegration time, dissolution, assay, and degradation products. Stability data for this product in the proposed marketing containers conforms to specifications. Based on the stability data provided the proposed expiration dating is acceptable.

3. Assessment of Bioequivalence

The manufacturer presented one fasting bioequivalence (BE) study comparing the test

product, Efavirenz Capsules 200 mg, to the reference listed drug (RLD), Sustiva ® Capsules 200 mg (Bristol Myers Squibb), and comparative dissolution data on both products. Statistical analysis of plasma concentration data for efavirenz demonstrate bioequivalence. The USFDA Office of Generic Drugs Division of Bioequivalence found the data and application acceptable with no deficiencies.

4. Summary of Product Safety and Efficacy

4.1 Introduction

Background
Efavirenz Capsules 50 mg, 100 mg, and 200 mg have been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's product. According to the submitted data on quality and bioavailability it is pharmacologically and therapeutically equivalent and thus interchangeable with the innovator product Sustiva®, for which benefits have been proven in terms of clinical efficacy.

Product Design
The development strategy for Efavirenz Capsules 50 mg, 100 mg, and 200 mg focused on the compatibility of the active ingredient with the excipients identified to match the dissolution profile of the innovator, thus producing a robust formulation.

Approved Indication
Efavirenz is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

Clinical Pharmacology

Pharmacodynamics

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a conformational change that causes a disruption of the enzyme's catalytic site. The activity of efavirenz does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not
inhibited by efavirenz.

Pharmacokinetics

Absorption and Bioavailability: Oral bioavailability is 40% to 45% without food. Fat-containing meals increase absorption significantly. Peak efavirenz plasma concentrations of 1.6 - 9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers.

Distribution: Efavirenz is highly bound (approximately 99.5 - 99.75%) to human plasma proteins, predominantly albumin. The proportion is approximately 3-fold higher than the nonprotein-bound (free) fraction of efavirenz in plasma.

Metabolism / Elimination: 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.

Refer to the Summary of Product Characteristics (SPC), Part 4 of this Public Assessment Report, for more extensive discussion of absorption, bioavailability, distribution, metabolism, and elimination data for Efavirenz Capsules.

Drug Interactions, related side effects and contraindications

Efavirenz is contraindicated in patients with clinically significant hypersensitivity to efavirenz or to any of the components contained in the formulation.

Efavirenz is an inducer of the hepatic enzyme CYP3A4 and an inhibitor of some CYP isozymes including CYP4A. It is therefore possible that coadministration of efavirenz with medicinal products which affect CYP3A4 (such as astemizole, terfenadine, cisapride, midazolam, triazolam, ergot derivatives and St. John's wort) or food (such as grapefruit juice) which affect CYP3A4 activity may result in an alteration in the plasma concentration of either agent. (Note: astemizole, terfenadine, and cisapride are no longer marketed in the U.S., Canada, or Europe, but are available in many countries, including in many PEPFAR focus countries.)

See the Summary of Product Characteristics (Part 4, Section 4.5) in this Public Assessment Report for extensive discussion of drug interactions and other forms of interaction.

Clinical Efficacy

Efavirenz has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs. These studies have demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with other nucleoside analogue(s) and/or a PI. In recent studies by intention to-treat analysis > 70% of subjects have achieved plasma HIV RNA < 50 copies/mL after 48 weeks of combination treatment that included efavirenz with other antiretroviral drugs.

HIV-1 resistance to efavirenz involves the development of mutations in the reverse transcriptase gene at positions 100, 103, 106, 108, 181, 188 and 190. The K103N or Y188L mutation alone prevents the clinical utility of efavirenz. The V106M mutation is more common in HIV-1 subtype C than subtype B.

Rapid emergence of resistance to NNRTIs, including efavirenz, is likely to occur in case of virological failure. Patients who are infected with known efavirenz-resistant HIV or patients who have previously experienced virological failure on a efavirenz- or nevirapine-containing regimen may not respond sufficiently to further treatment with a combination regimen containing efavirenz or nevirapine.

Clinical studies in special populations

Liver Disease
No dose adjustment is necessary for mild to moderate liver impairment but discontinuation may be necessary for severe liver impairment.

Renal Impairment
No dose modification is needed.

Clinical Safety

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV infection with efavirenz. The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Metabolic and nutrition disorders
Very common: increased fasting triglycerides, total cholesterol, high- and low-density lipoprotein cholesterol
Common: gynecomastia

Nervous system disorders
Very common: headache, confusion, dizziness, insomnia, somnolence, impaired concentration, abnormal dreaming
Common: anxiety and depression
Uncommon: psychosis (increased likelihood in those with history of psychiatric disease)

Hepatobiliary disorders
Common: elevation of liver enzymes

Skin and subcutaneous tissue disorders
Very common: rash

General disorders
Very common: fatigue

5. Overall Conclusion and benefit risk assessment

Quality
The quality of Efavirenz Capsules 50 mg, 100 mg, and 200 mg is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics (Part 4 of this Public Assessment Report). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence
Efavirenz Capsules 50 mg, 100 mg, and 200 mg have been shown to be bioequivalent to the comparator product, Sustiva® Capsules 50 mg, 100 mg, and 200 mg.

Efficacy and Safety
Regarding clinical efficacy and safety, efavirenz is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics (Part 4 of this Public Assessment Report) are taken into consideration.

Benefit Risk Assessment
Based on USFDA assessment of data on quality, bioequivalence, safety, and efficacy, the benefit risk profile of Efavirenz Capsules 50 mg, 100 mg, and 200 mg was considered acceptable for the following indication: HIV-1 infection in combination with other antiretroviral agents.

Products added to the WHO prequalification list on the basis of USFDA tentative approval rely on scientific assessment and inspections conducted by the USFDA. A product listed as USFDA **tentatively approved** indicates that although existing patents and/or other marketing exclusivity prevent marketing of this product in the USA, the product meets all of USFDA's safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

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