Application for Inclusion of EFAVIRENZ 600 MG On WHO Model List of Essential Medicines

Submitted By

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1. **Summary statement of the proposal for inclusion:**

   Proposition to add a new strength for an already listed Essential Medicine:

   Efavirenz **600 MG** Tablet

   Efavirenz (EFV) is an antiretroviral medicine belonging to the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) class. The following strengths are already included in the Essential Medicines List, 14th Edition (March 2005)
   Efavirenz 50,100 and 200mg capsules.
   Efavirenz 150mg/5ml Oral Solution.

   In the current practice, efavirenz 600mg one tablet a day has replaced efavirenz 200mg three capsules a day for the treatment of HIV-1 infection of adults in combination with other antiretroviral drugs.

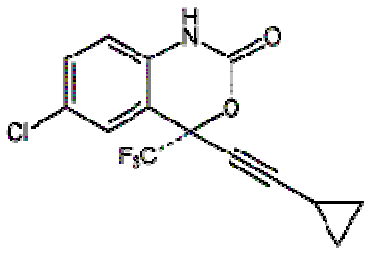
2. **Name of the focal point in WHO supporting the application:**
   Charlie Gilks
   HIV/AIDS Department
   World Health Organisation

3. **Name of the organization(s) consulted and/or supporting the application:**
   Not applicable

4. **International Non-Proprietary Name:**
   Efavirenz

5. Formulation proposed for inclusion:

Drug Substance
Efavirenz
CAS Registry Number: 154598-52-4
CAS Name: (4*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one
Molecular Formula: $C_{14}H_9ClF_3NO_2$
Molecular Weight: 315.67



Drug Product
Film-coated tablet containing 600mg efavirenz.
List of excipients
Tablet core:
Croscarmellose sodium, Microcrystalline cellulose, Sodium laurilsulfate, Hydroxypropylcellulose, Lactose monohydrate and Magnesium stearate
Film coating:
Hypromellose (E464), Titanium dioxide (E171), Macrogol 400, Yellow iron oxide (E172), Carnauba wax

6. International availability

Efavirenz 600mg is available worldwide on either STOCRIN (MSD) or SUSTIVA (BMS) trademarks.

Manufacturer of the Drug Product
Manufacturing, Packaging and Quality Control:
Merck Sharp & Dohme (Australia) Pty Ltd.
54-68 Ferndell Street
South Granville, NSW 2142 Australia

Stability Testing:
Merck Sharp & Dohme Ltd.
Shotton Lane, Cramlington
Northumberland NE23 3JU
England

Alternate Packaging Sites:
Merck Sharp & Dohme BV
Waarderweg 39 2031 BN, Haarlem
The Netherlands

Merck Sharp & Dohme de Mexico S.A de C.V.
Ave Division del Norte 3377. Col. Xotepingo
C.P. 04610 Mexico, D.F.

Merck Sharp & Dohme (I.A.) Corp.
Urbanizacion Industrial Rohrmoser
100 Metros Sur Embajada Americana. Pavas, San Jose
Costa Rica

MSD (Pty) Ltd.
16th Road/Private Bag 3
Halfway House, 1685
Midrand, South Africa

Packaging Source of Supply for Efavirenz Tablets
Europe / Middle East, Northern & Central Africa /Asia/Pacific
MSD (Australia) Pty. Ltd.
MSD BV

Southern Africa MSD (Australia) Pty. Ltd.
MSD (South Africa) Pty Ltd.
MSD BV

Brazil, Argentina, and Mexico
MSD (Australia) Pty. Ltd.
MSD Mexico S.A. de C.V.

Central & South America/Caribbean (excluding Brazil, Argentina and Mexico)
MSD (Australia) Pty. Ltd.
MSD (I.A.) Corp.

7. **Listing Type Requested:**
Listing is requested on the Model List of Essential Medicines, antiretroviral medicines as an example of the therapeutic class of Non-Nucleoside Reverse Transcriptase Inhibitors **(NNRTI)*:***

Proposed (new/adapted) text for the essential Medicines – WHO Model List:

"6.4.2.2 Non-Nucleoside Reverse Transcriptase Inhibitors

efavirenz (EFVor EFZ)	capsule, 50 mg, 100 mg, 200 mg **tablet 600 mg** oral solution, 150 mg/5ml"

8. Information supporting the public health relevance of the submission

8.1 Epidemiological information on disease burden

Since the first clinical evidence of AIDS was reported over 25 years ago, an estimated 25 million people have died as a result of HIV infection, making it one of the most destructive epidemics in recorded history.[1] In 2005, there were an estimated 3.1 million deaths due to AIDS. Current estimates suggest that some 40.3 million people worldwide are infected with HIV, up from an estimated 37.5 million in 2003, and twice as many as compared to 1995. In 2005, it is estimated that an additional 4.9 million individuals worldwide became infected with HIV, and 700,000 of these new infections were in children <15 years of age.

Of major concern is the prevalence of HIV/AIDS in developing countries. Approximately 95% of all HIV-infected people live in low- and middle-income countries.[2] Although there is new evidence that adult HIV infection rates have decreased in certain countries, the overall trends in HIV transmission are still increasing, and the overall number of people living with HIV has continued to increase in all regions of the world except the Caribbean.[3]

The steepest increases in HIV infections have occurred in Eastern Europe and Central Asia, and in East Asia. In Eastern Europe and Central Asia, there was a 25% increase in the number of people living with HIV (to 1.6 million) since 2003, and AIDS death rates almost doubled (to 62,000) during that time.[1] In East Asia there was a 20% increase in the number of people living with HIV (to 870,000) since 2003. However, the worst affected area is Sub-Saharan Africa, with 64% of new infections (3.2 million) occurring here and with an estimated 2.4 million who died of HIV-related illnesses in 2005.[1, 3]

Without HIV prevention measures, about 35% of children born to HIV-positive women will contract the virus.[1] In many countries, life expectancy and child survival rates have plummeted. For example, in seven African countries where HIV prevalence is >20%, the average life expectancy of a person born between 1995 and 2000 is now 49 years, which is 13 years lower than in the absence of AIDS.[4]

In countries already burdened by huge socio-economic challenges, HIV/AIDS threatens human social welfare, developmental progress and social stability on an unprecedented scale. HIV/AIDS continues to cripple the economic development of entire countries, because it often strikes people during their most productive period of life.[5] For example, of the 14,000 persons who became infected each day in 2005, about 12,000 (86%) were aged 15 to 49 years.[2] Overall, young people aged 15 to 24 years account for about half of all new HIV infections per day worldwide.[2]

8.2 Assessment of current use

The antiretroviral drugs do not cure the HIV infection; they only temporarily suppress viral replication and improve symptoms. They have various adverse effects and patients receiving these drugs require careful monitoring by adequately trained health professionals. For these reasons, continued rigorous promotion of measures to prevent new infections is essential and the need for this has not been diminished in any way by the addition of antiretroviral drugs. Adequate resources and trained health professionals are a prerequisite for the introduction of this class of drugs. Effective therapy requires commencement of three or four drugs simultaneously, and alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in the case of toxicity, or to replace failing regimens. The use of fixed-dose combinations can help simplify treatment, facilitate storage and distribution, and improve patients' adherence to the treatment plan.

The introduction of potent antiretroviral agents and the combined use of these drugs have markedly reduced the replication of HIV in many patients, and improved survival rates.[6] The primary goals of antiretroviral therapy are to reduce HIV-related morbidity and mortality, improve quality of life, restore and preserve immunologic function, and maximally and durably suppress viral load.[7] Plasma viremia is a strong prognostic indicator of HIV disease progression. Reductions in plasma viremia achieved with antiretroviral therapy account for substantial clinical benefits. Therefore, suppression of plasma viremia as much as possible for as long as possible is a critical goal of antiretroviral therapy.[7]The standardization and simplification of treatment and monitoring continues to be the prime consideration underpinning WHO recommendations for the use of ART, in order to widen access to effective therapy in resource-limited settings where individualized patient management by physicians specialized in HIV medicine is not feasible. Standardized clinical and, where available, immunological (CD4) evaluation to guide the initiation of ART, the use of appropriate formulations, including fixed- dose combinations (FDCs) of ARVs, simple laboratory tools and a symptom-directed approach to monitoring adverse events, are keys to the simplified approach.[8] WHO recommends that the first-line regimen for adults and adolescents contain two NRTIs plus one NNRTI in resource-limited settings (except for HIV-2 infections that are naturally resistant to NNRTIs), based on available evidence, clinical experience and programmatic feasibility for the wider introduction of ART.[8] The thiacytadine analogues (3TC or FTC) are pivotal to first-line regimens. 3TC or FTC should be used with a companion nucleoside or nucleotide analogue, the choices here being AZT, TDF, ABC or d4T.The preferred NRTI backbone is composed of AZT or TDF combined with either 3TC or FTC .Finally an NNRTI, either efavirenz or nevirapine should be added - both should be available for mutual substitution for toxicity and for issues related to drug choice in pregnancy and TB [8] (Table 1).

Table 1. WHO recommended first-line and second-line regimen in resource-limited settings in 2006

FIRST-LINE REGIMEN		SECOND-LINE REGIMEN	
		RTI COMPONENT	PI COMPONENT [a]
STANDARD STRATEGY	AZT or d4T + 3TC [b] + NVP or EFV	ddI + ABC or TDF + ABC or TDF + 3TC (± AZT) [c]	PI/r [d]
	TDF + 3TC [b] + + NVP or EFV	ddI + ABC or ddI + 3TC (± AZT) [c]	
	ABC + 3TC [b] + + NVP or EFV	ddI + 3TC (± AZT) [c] or TDF + 3TC (± AZT) [c]	
ALTERNATIVE STRATEGY	AZT or d4T + 3TC [b] + TDF or ABC	EFV or NVP ± ddI	

a NFV does not need refrigeration and can be used as a PI alternative in places without a cold chain.

b 3TC and FTC are considered interchangeable because they are structurally related and share pharmacological properties and resistance profiles.

c 3TC can be considered to be maintained in second-line regimens to potentially reduce viral fitness, confer residual antiviral activity and maintain pressure on the M184V mutation to improve viral sensitivity to AZT or TDF. AZT may prevent or delay the emergence of the K65R mutation.

d There are insufficient data to detect differences among currently available RTV-boosted PIs (ATV/r, FPV/r, IDV/r, LPV/r and SQV/r) and the choice should be based on individual programme priorities (see text). In the absence of a cold chain, NFV can be employed as the PI component but it is considered less potent than an RTV-boosted PI.

Aligned with several European guidelines [9, 10], the US Department of Health and Human Services (DHHS) recommends efavirenz as the preferred NNRTI to use in combination with 2 NRTIs for the treatment of HIV-1 infection in treatment naïve patients [7] (Table 2).

Table 2. DHHS Antiretroviral Components Recommended for Treatment of HIV-1 Infection in Treatment Naïve Patients [7]

To Construct an Antiretroviral Regimen,
Select 1 Component from Column A + 1 from Column B

	Column A		**Column B**
	NNRTI	**PI**	**2 NRTIs**
Preferred (alphabetical order)	Efavirenz	Atazanavir + ritonavir Fosamprenavir + ritonavir BID Lopinavir/ritonavir BID	Tenofovir/emtricitabine Zidovudine/lamivudine
Alternative (alphabetical order)	Nevirapine (unboosted)	Atazanavir Fosamprenavir (unboosted) Fosamprenavir + ritonavir QD Lopinavir/ritonavir QD	Abacavir/lamivudine Didanosine + lamivudine

Because of a lower pill burden, efavirenz 600 has replaced Efavirenz 200 for the treatment of HIV-1 infection in adults.
Efavirenz 600 is included in the list of products recommended by WHO as being acceptable in principle for procurement by UN Agencies.[11]

8.3 Target population

Efavirenz 600 is indicated in antiviral combination treatment of HIV-1 infected adults and adolescents weighing above 40kg.[12] Efavirenz is not indicated in case of HIV-2 infection.[12]

Pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. Efavirenz should not be used during pregnancy unless there is no other appropriate treatment option.[12]

Efavirenz (EFV) is the NNRTI recommended by WHO as initial option in case of HIV/tuberculosis co-infection.[8] EFV blood levels are decreased in the presence of rifampicin. This can be overcome by a dose increase of 600 mg to 800 mg daily as recommended by MSD. However emerging evidence does not show any benefit in increasing the EFV dose to 800 mg/daily in patients weighing under 60 kg and receiving both EFV and rifampicin. While awaiting more data on EFV dosing for persons weighing 60 kg and above, WHO recommends the standard 600-mg dose of EFV.[8]
EFV is the NNRTI recommended by WHO in case of HIV/HBV co-infection.[8]

As the relatively high cost of medicines was a factor limiting access to ARVs in developing countries, in May 2000 five UN organizations (the United Nations Population Fund [UNFPA], United Nations Children's Fund [UNICEF], World Health Organization [WHO], World Bank and UNAIDS Secretariat) entered into a partnership with five pharmaceutical companies (Boehringer Ingelheim GmbH; Bristol-Myers Squibb; GlaxoSmithKline; Merck & Co., Inc.; and F. Hoffmann-La Roche Ltd. – later joined by Abbott Laboratories and Gilead Sciences) to address the affordability of HIV medicines and to work together to increase access to HIV/AIDS care and treatment in developing countries.[13] Since then, the cost of ARV drugs offered individually by the pharmaceutical partners in the Accelerating Access Initiative (AAI) for the least developed countries has decreased significantly, in some cases to 10–20% of their price in industrialized countries.[13] Within AAI, efavirenz 600 has been made available at reduced price in the developing countries.

9. Treatment details:

Indication: Efavirenz is indicated in antiviral combination treatment of HIV-1 infected adults, adolescents and children 3 years of age and older.[12]
It is recommended that STOCRIN be taken on an empty stomach. [12]

Adults: the recommended dosage of STOCRIN in combination with nucleoside analogue reverse transcriptase inhibitors (NRTIs) with or without a PI is 600 mg orally, once daily.

Adolescents and children (3 to 17 years): the recommended dose of STOCRIN in combination with a PI and/or NRTIs for patients between 3 and 17 years of age is described in Table 3. STOCRIN tablets must only be administered to children who are able to reliably swallow tablets. STOCRIN is not recommended for use in children below the age of 3 years or weighing less than 13 kg due to a lack of data on safety and efficacy in that age group. [12]

Table 3 Paediatric dose to be administered once daily [12]

Body Weight kg	STOCRIN 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

* STOCRIN 50 mg, 200 mg and 600 mg film-coated tablets are available.

Elderly: insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients. [12]

Renal insufficiency: the pharmacokinetics of efavirenz has not been studied in patients with renal insufficiency; however, less than 1 % of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal. [12]

Liver disease: patients with mild to moderate liver disease may be treated with their normally recommended dose of efavirenz. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. [12]

10. Comparative effectiveness in clinical settings:

Two controlled studies (006 [14] and ACTG 364 [15]) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naïve and NRTI-experienced HIV-infected patients. In these studies the dose of efavirenz was 600 mg once daily; the dose of indinavir was 1,000 mg every 8 hours when used with efavirenz and 800 mg every 8 hours when used without efavirenz. The dose of nelfinavir was 750 mg given three times a day. The standard doses of NRTIs given every 12 hours were used in each of these studies.

Study 006 [14], a randomized, open-label trial, compared efavirenz + zidovudine + lamivudine or efavirenz + indinavir with indinavir + zidovudine + lamivudine in 1,266 patients who were required to be efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The mean baseline CD4 cell count was 341 cells/mm^3 and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 4. In the analysis of responder rates (the non-completer equals failure analysis [NC = F]), patients who terminated the study early for any reason, or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 50 or above 400 copies/ml at the missing time points.

Table 4 : Efficacy results for study 006 [14]

		Responder rates (NC = F[a]) Plasma HIV-RNA		Mean change from baseline-CD 4 cell count cells/mm^3 (S.E.M.[c])
		< 400 copies/ml (95 % C.I.[b])	< 50 copies/ml (95 % C.I.[b])	
Treatment Regimen[d]	n	48 weeks	48 weeks	48 weeks
EFV + ZDV + 3TC	202	67 % (60 %, 73 %)	62 % (55 %, 69 %)	187 (11.8)
EFV + IDV	206	54 % (47 %, 61 %)	48 % (41 %, 55 %)	177 (11.3)
IDV + ZDV + 3TC	206	45 % (38 %, 52 %)	40 % (34 %, 47 %)	153 (12.3)

[a] NC = F, noncompleter = failure.
[b] C.I., confidence interval.
[c] S.E.M., standard error of the mean.
[d] EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir.

Long-term results at 168 weeks of study 006 (160 patients completed study on treatment with EFV +IDV, 196 patients with EFV + ZDV + 3TC and 127 patients with IDV + ZDV + 3TC, respectively), suggest durability of response in terms of proportions of patients with HIV RNA < 400 copies/ml, HIV RNA < 50 copies/ml and in terms of mean change from baseline CD4 cell count.

Efficacy results for study ACTG 364 are found in Table 5. Study ACTG 364 enrolled 196 patients who had been treated with NRTIs but not with PIs or NNRTIs.

Table 5: Efficacy results for studies ACTG 364 [15]

		Responder rates (NC = F[a]) Plasma HIV-RNA				Mean change from baseline-CD4 cell count	
Study Number/ Treatment Regimens[b]	n	%	(95 % C.I.[c])	%	(95 % C.I.)	cells/mm^3	(S.E.M.[d])
Study ACTG 364 48 weeks		< 500 copies/ml		< 50 copies/ml			
EFV + NFV + NRTIs	65	70	(59, 82)	---	---	107	(17.9)
EFV + NRTIs	65	58	(46, 70)	---	---	114	(21.0)
NFV + NRTIs	66	30	(19, 42)	---	---	94	(13.6)

[a] NC = F, noncompleter = failure.
[b] EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir.
[c] C.I., confidence interval for proportion of patients in response.
[d] S.E.M., standard error of the mean.
---, not performed.

A prospective open-label one-arm study study has been performed in Senegal [16] to evaluate the effectiveness, adherence and tolerance of a once-a-day
highly active antiretroviral therapy regimen in adults.40 treatment-naïve HIV-1-infected patients took the following three drugs once a day at bedtime:
didanosine, lamivudine and efavirenz.
Results: Eighty-five per cent of patients were at Centers for Disease Control and Prevention stage B or C and the plasma HIV RNA level was 5.4 $\pm$0.4 log10 copies/ml at baseline. The percentage of patients with plasma HIV-1 RNA below 500 copies/ml at 6 months was 95% [95% confidence interval (CI), 83–99]. The proportions of patients with plasma HIV-1 RNA below 50 copies/ml at months 3, 6, 9, 12 and 15 were 26% (n = 39; 95% CI, 12–39), 78% (n = 40; 95% CI, 65–90), 70% (n = 40; 95% CI, 56–84), 77% (n = 39; 95% CI, 64–90) and 69% (n = 39; 95% CI, 55–84), respectively. The CD4 cell count was 164 $\pm$ 75x10^6/l at baseline and increased by a mean of 199 $\pm$ 101x10^6/l at month 15. Permanent treatment discontinuation was never necessary for serious adverse effects. Adherence was excellent, as shown by plasma drug concentrations and according to the results of the questionnaire.
Conclusions: The once-daily regimen of didanosine, lamivudine and efavirenz was safe, easy-to-take and demonstrated strong antiretroviral and immunologic effects in African patients with advanced HIV infection.

11. Comparative Evidence on Safety:

Warnings and Precautions for Use

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

When prescribing medicinal products concomitantly with efavirenz, physicians should refer to the corresponding Summary of Product Characteristics.

Patients should be advised that current antiretroviral therapy, including efavirenz, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

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

Rash: mild-to-moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1 % of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1 %. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus.

Rash was reported in 26 of 57 children (46 %) treated with efavirenz during a 48-week period and was severe in three patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Patients who discontinued treatment with other NNRTIs due to rash may be at higher risk of developing rash during treatment with efavirenz.

Psychiatric symptoms: psychiatric adverse experiences have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. 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.

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 efavirenz 600 mg daily in clinical studies. 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 common 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 rarely in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz. Caution must be taken in any patient with a history of seizures.

Effect of food: the administration of efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of undesirable effects. It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime.

Immune Reactivation Syndrome: in HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Special populations:

Liver disease: 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 efavirenz to patients with mild-to-moderate liver disease. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals.

The safety and efficacy of efavirenz has not been established in patients with significant underlying liver disorders. Efavirenz is contraindicated in patients with severe hepatic impairment. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. 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. If there is evidence of 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 efavirenz needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered.

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

Renal insufficiency: The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1 % of an efavirenz dose 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: insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.

Children: efavirenz has not been evaluated in children below 3 years of age or who weigh less than 13 kg. Therefore, efavirenz should not be given to children less than 3 years of age.

Lactose: this medicinal product contains 250 mg of lactose in each 600-mg daily dose. This quantity is not likely to induce symptoms of lactose intolerance.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Individuals with these conditions may take efavirenz oral solution, which is free from lactose.

Undesirable Effects

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported treatment-related undesirable effects of at least moderate severity reported in at least 5 % of patients were rash (11.6 %), dizziness (8.5 %), nausea (8.0 %), headache (5.7 %) and fatigue (5.5 %). The most notable undesirable effects associated with efavirenz are rash and nervous system symptoms. The administration of efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of undesirable effects.

The long-term safety profile of efavirenz-containing regimens was evaluated in a controlled trial (006) in which patients received efavirenz + zidovudine + lamivudine (n = 412, median duration 180 weeks), efavirenz + indinavir (n = 415, median duration 102 weeks), or indinavir + zidovudine + lamivudine (n = 401, median duration 76 weeks). Long-term use of efavirenz in this study was not associated with any new safety concerns.

Rash: in clinical studies, 26 % of patients treated with 600 mg of efavirenz experienced skin rash compared with 17 % of patients treated in control groups. Skin rash was considered treatment related in 18 % of patients treated with efavirenz. Severe rash occurred in less than 1 % of patients treated with efavirenz, and 1.7 % discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1 %.

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with efavirenz. In most patients rash resolves with continuing therapy with efavirenz within one month. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when efavirenz is restarted.

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz, and two discontinued because of rash.

Psychiatric symptoms: serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1,008 patients treated with regimens containing efavirenz for an average of 1.6 years and 635 patients treated with control regimens for an average of 1.3 years, the frequency of specific serious psychiatric events are detailed hereafter:

	Merck Sharp & Dohme Interpharma	
	Efavirenz regimen	Control regimen
- severe depression	1.6 %	0.6 %
- suicidal ideation	0.6 %	0.3 %
- non-fatal suicide attempts	0.4 %	0 %
- aggressive behaviour	0.4 %	0.3 %
- paranoid reactions	0.4 %	0.3 %
- manic reactions	0.1 %	0 %

Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences with the frequency of each of the above events ranging from 0.3 % for manic reactions to 2.0 % for both severe depression and suicidal ideation. There have also been post-marketing reports of death by suicide, delusions and psychosis-like behaviour.

Nervous system symptoms: in clinical controlled trials, frequently reported undesirable effects in patients receiving 600 mg efavirenz with other antiretroviral agents included, but were not limited to: dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms of moderate-to-severe intensity were experienced by 19.4 % of patients compared to 9.0 % of patients receiving control regimens. These symptoms were severe in 2.0 % of patients receiving efavirenz 600 mg daily and in 1.3 % of patients receiving control regimens. In clinical studies 2.1 % of patients treated with 600 mg of efavirenz discontinued therapy because of nervous system symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. In one clinical study, the monthly prevalence of nervous system symptoms of at least moderate severity between weeks 4 and 48, ranged from 5 % - 9 % in patients treated with regimens containing efavirenz and 3 % - 5 % in patients treated with the control regimen. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Nervous system symptoms may occur more frequently when efavirenz is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms and can be recommended during the first weeks of therapy and in patients who continue to experience these symptoms. Dose reduction or splitting the daily dose has not been shown to provide benefit.

Analysis of long-term data from study 006 (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with efavirenz + zidovudine + lamivudine, efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the control arm.

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed

below. Frequency is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000) including isolated reports.

Immune system disorders
uncommon: hypersensitivity

Psychiatric disorders
common: anxiety, depression
uncommon: affect lability, aggression, euphoric mood, hallucination, mania, paranoia, suicide attempt, suicide ideation

Nervous system disorders
common: abnormal dreams, disturbance in attention, dizziness, headache, insomnia, somnolence
uncommon: agitation, amnesia, ataxia, coordination abnormal, confusional state, convulsions, thinking abnormal

Eye disorders
uncommon: vision blurred

Ear and labyrinth disorders
uncommon: vertigo

Gastrointestinal disorders
common: abdominal pain, diarrhoea, nausea, vomiting
uncommon: pancreatitis acute

Hepatobiliary disorders
uncommon: hepatitis acute

Skin and subcutaneous tissue disorders
very common: rash
common: pruritus
uncommon: erythema multiforme

General disorders and administration site conditions
common: fatigue

Immune Reactivation Syndrome: in HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Laboratory test abnormalities:

Liver enzymes: elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to greater than five times the upper limit of the normal range (ULN) were seen in 3 % of 1,008 patients treated with 600 mg of efavirenz (5 - 8 % after long-term treatment in study 006). Similar elevations were seen in patients treated with control regimens (5 % after long-term treatment). Elevations of gamma-glutamyltransferase (GGT) to greater than five times ULN were observed in 4 % of all patients treated with 600 mg of efavirenz and 1.5 - 2 % of patients treated with control regimens (7 % of efavirenz-treated patients and 3 % of control-treated patients after long-term treatment). Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction. In the long-term study (006), 1 % of patients in each treatment arm discontinued because of liver or biliary system disorders.

In the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, elevations in AST to greater than five times ULN developed in 13 % of patients in the efavirenz arms and 7 % of those in the control arm, and elevations in ALT to greater than five times ULN developed in 20 % of patients in the efavirenz arms and 7 % of the patients in the control arm. Among co-infected patients, 3 % of those treated with efavirenz-containing regimens and 2 % in the control arm discontinued from the study because of liver or biliary system disorders. Reasons for discontinuation among co-infected recipients of efavirenz included abnormalities in hepatic enzymes; there were no discontinuations reported in this study for cholestatic hepatitis, hepatic failure, or fatty liver.

Amylase: in the clinical trial subset of 1,008 patients, asymptomatic increases in serum amylase levels greater than 1.5 times the upper limit of normal were seen in 10 % of patients treated with efavirenz and 6 % of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown.

Lipids: increases in total cholesterol of 10 - 20 % have been observed in some uninfected volunteers receiving efavirenz. In clinical trials of various efavirenz-containing regimens in treatment naive patients, total cholesterol, HDL-cholesterol, and triglycerides increased over 48 weeks of treatment (21 – 31 %, 23 – 34 %, and 23 – 49 %, respectively). The proportion of patients with a total cholesterol/HDL-cholesterol ratio greater than 5 was unchanged. The magnitude of changes in lipid levels may be influenced by factors such as duration of therapy and other components of the antiretroviral regimen.

Cannabinoid test interaction: efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers

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

Postmarketing experience with efavirenz has shown the following additional adverse events to occur in association with efavirenz-containing antiretroviral treatment regimens: delusion, gynaecomastia, hepatic failure, neurosis, photoallergic dermatitis, psychosis and completed suicide.

Adolescents and children: undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (in a clinical study including 57 children who received efavirenz during a 48-week period, rash was reported in 46 %) and was more often of higher grade than in adults (severe rash was reported in 5.3 % of children). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered. Although nervous system symptoms are difficult for young children to report, they appear to be less frequent in children and were generally mild. In the study of 57 children, 3.5 % of patients experienced nervous system symptoms of moderate intensity, predominantly dizziness. No child had severe symptoms or had to discontinue because of nervous system symptoms.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

An economic model of first-line antiretroviral (ARV) strategies in ARV-naïve patients has compared ARV drug cost of a fixed-dose combination (FDC) of nevirapine (NVP) to an efavirenz (EFV) – based regimen in Thailand. [17] *Methods:* An economic model was developed to project the overall ARV drug cost of the 2 alternative 1st-line strategies over a 2-year time frame in ARV treatment-naïve patients. If treatment fails, patients could progress to a 2nd-line ARV therapy and remain on the 2nd-line therapy for the rest of the modeled period. Treatment failure rates of NVP and EFV-based regimens, base case CD4 count and viral load testing frequency (every 3 months), as well as patient characteristics were obtained from a previously published cohort study. Prices (in US$) of ARV therapies and tests used in the model were obtained from the 2003 WHO/MSF Surmounting Challenges guide and followed Thai treatment guidelines. *Results:* At 2 years, the estimated total ARV drug cost of the 1st-line strategy using a FDC of NVP was $2,179/patient, whereas the total ARV drug cost was $1,568/patient for the EFV-based strategy. The difference in total ARV drug cost between the two 1st-line strategies was $611/patient.*Conclusions:* The model suggests that a 1st-line strategy using an EFV-based regimen could be cost-saving and/or allow more patients to be treated over 2 years in Thailand when compared to a strategy using NVP. Policy makers, governments, and NGOs should consider more than just the drug cost of 1stline therapies when setting ARV treatment guidelines as patients initiating a therapy with higher treatment failure rate would require more expensive salvage therapies sooner than if they had initiated a therapy with a much lower failure rate. [17]

12.1 Range of costs of the proposed medicine

12.1.1 United States of America

STOCRIN® 600 MG/Pack of 30's capsules is not available in the United States of America

12.1.2 Developing Countries

STOCRIN® 600 MG (efavirenz,)/Pack of 30's capsules is commercialized by MSD as follow:
- Low HDI countries or Medium HDI countries with adult HIV prevalence of 1% or greater: Ex-MSD: $22.80
- Medium HDI countries with adult HIV prevalence of less than 1%: Ex-MSD: $57.30

HDI levels defined as per enclosed reference
http://hdr.undp.org/statistics/data/indicators.cfm?x=79&y=1&z=1

13. Summary of regulatory status of the medicine (in country of origin and preferably in other countries as well):

Efavirenz 600mg is registered and available – under STOCRIN (MSD) and/or SUSTIVA(BMS) trademarks - in the following countries:

Country	**Approval Date**
Argentina	August 08, 2002
Aruba	July 15, 2003
Australia	**August 15, 2002**
Austria	August 23, 2002
Belgium	August 23, 2002
Benin	February 04, 2004
Bolivia	June 09, 2003
Botswana	January 30, 2004
Brazil	September 19, 2002
Bulgaria	January 20, 2003
Burkina Faso	February 18, 2003
Burundi	March 17, 2003
Central African Republic	June 07, 2004
Cameroon	November 13, 2003
Chile	October 21, 2003
China	August 05, 2003
Colombia	June 05, 2003
Congo	April 22, 2004
Cyprus	August 23, 2002
Democratic Republic of Congo	April 14, 2003
Costa Rica	January 28, 2003
Curacao	September 10, 2003
Czech Republic	August 23, 2002
Denmark	August 23, 2002
Dominican Republic	September 15, 2003
Ecuador	May 22, 2003
El Salvador	November 05, 2003
Estonia	August 23, 2002
Ethiopia	September 19, 2003
Finland	August 23, 2002
France	August 23, 2002
Gabon	December 16, 2002
Gambia	March 29, 2004
Germany	August 23, 2002
Ghana	June 25, 2003
Greece	August 23, 2002
Guatemala	June 03, 2003
Guinea	Oct 29, 2002
Honduras	June 18, 2003
Hong Kong	December 06, 2002
Hungary	August 23, 2002
Iceland	August 30, 2002
Ireland	August 23, 2002
Israel	October 26, 2003
Italy	August 23, 2002

Jamaica	August 26, 2003
Kenya	January 23, 2004
Kuwait	April 07, 2003
Latvia	August 23, 2002
Lithuania	August 23, 2002
Luxembourg	August 23, 2002
Madagascar	July 27, 2003
Malaysia	February 21, 2003
Malta	August 23, 2002
Mauritania	February 12, 2004
Mali	March 12, 2003
Malawi	July 13, 2005
Mauritius	April 16, 2003
Mexico	September 01, 2002
Morocco	September 25, 2003
Netherlands	**August 23, 2002**
New Zealand	October 25, 2001
Nicaragua	July 10, 2003
Nigeria	June 20, 2005
Namibia	August 18, 2004
Norway	September 30, 2002
Panama	January 30, 2004
Peru	November 11, 2002
Poland	August 23, 2002
Portugal	August 23, 2002
Qatar	February 19, 2004
Romania	January 20, 2003
Serbia and Montenegro	December 29, 2003
Singapore	August 30, 2002
Slovak Republic	August 23, 2002
Slovenia	August 23, 2002
South Africa	May 7, 2004
Spain	August 23, 2002
Sweden	August 23, 2002
Switzerland	May 16, 2002
Taiwan	December 11, 2002
Tanzania	June 04, 2004
Thailand	May 7, 2003
Togo	July 08, 2004
Tunisia	July 10, 2004
Trinidad	August 26, 2003
Turkey	September 1, 2006
Uganda	March 04, 2004
United Arab Emirates	May 23, 2003
United Kingdom	August 23, 2002
United States	**February 21, 2002**
Uruguay	April 22, 2003
Venezuela	May 08, 2003
Zambia	Dec 29, 2004

14. Availability of pharmacopoeial standards:

International Pharmacopoeia: Efavirenz monograph was adopted at the Fortieth WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2005 for addition to the 4th edition of the International Pharmacopoeia.

15. Proposed (new/adapted) text for the WHO Model Formulary:

WHO Model Formulary 2007 Efavirenz

EFV, EFZ

Capsules , efavirenz 50 mg, 100 mg, 200 mg

Tablets, Efavirenz, 600 mg

Oral solution , efavirenz 150 mg/5 ml

Uses:

Efavirenz 600mg is indicated in antiviral combination treatment of HIV-1 infected adults, adolescents above 40kg.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Grade C).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects [for example, cardiac arrhythmias, prolonged sedation or respiratory depression].

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

EFAVIRENZ must not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations.

Precautions:

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

When prescribing medicinal products concomitantly with efavirenz, physicians should refer to the corresponding Summary of Product Characteristics.

Patients should be advised that current antiretroviral therapy, including efavirenz, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

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

Rash: mild-to-moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1 % of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1 %. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus.

Rash was reported in 26 of 57 children (46 %) treated with efavirenz during a 48-week period and was severe in three patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Patients who discontinued treatment with other NNRTIs due to rash may be at higher risk of developing rash during treatment with efavirenz.

Psychiatric symptoms: psychiatric adverse experiences have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. 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.

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 efavirenz 600 mg daily in clinical studies. 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 common 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 rarely in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz. Caution must be taken in any patient with a history of seizures.

Effect of food: the administration of efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of undesirable effects. It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime.

Immune Reactivation Syndrome: in HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Special populations:

Liver disease: 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 efavirenz to patients with mild-to-moderate liver disease. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals.

The safety and efficacy of efavirenz has not been established in patients with significant underlying liver disorders. Efavirenz is contraindicated in patients with severe hepatic impairment. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. 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. If there is evidence of 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 efavirenz needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered.

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

Renal insufficiency: the pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1 % of an efavirenz dose 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: insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.

Children: efavirenz has not been evaluated in children below 3 years of age or who weigh less than 13 kg. Therefore, efavirenz should not be given to children less than 3 years of age.

Lactose: this medicinal product contains 250 mg of lactose in each 600-mg daily dose. This quantity is not likely to induce symptoms of lactose intolerance.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Individuals with these conditions may take efavirenz oral solution, which is free from lactose.

Dosage:

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

Concomitant antiretroviral therapy: Efavirenz must be given in combination with other antiretroviral medicines.

It is recommended that efavirenz be taken on an empty stomach. The increased efavirenz concentrations observed following administration of efavirenz with food may lead to an increase in frequency of adverse events.
In order to improve the tolerability of nervous system undesirable effects, bedtime dosing is recommended.

*Adults***:** the recommended dosage of efavirenz in combination with nucleoside analogue reverse transcriptase inhibitors (NRTIs) with or without a PI is 600 mg orally, once daily.

Adolescents and children (3 to 17 years): the recommended dose of efavirenz in combination with a PI and/or NRTIs for patients between 3 and 17 years of age is described in Table 1. Efavirenz tablets must only be administered to children who are able to reliably swallow tablets. Efavirenz is not recommended for use in children below the age of 3 years or weighing less than 13 kg due to a lack of data on safety and efficacy in that age group.

Paediatric 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

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

Liver disease: patients with mild to moderate liver disease may be treated with their normally recommended dose of efavirenz. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms.

Interaction with other medicinal products and other forms of interaction

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP isozymes including CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.
Efavirenz must not be administered concurrently with terfenadine, astemizole, 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.

Concomitant antiretroviral agents:

Protease Inhibitors:

Amprenavir: although efavirenz has been seen to decrease the C_{max}, AUC and C_{min} of

amprenavir by approximately 40 % in adults, when amprenavir is combined with ritonavir, the effect of efavirenz is compensated by the pharmacokinetic booster effect of ritonavir. Therefore, if efavirenz is given in combination with amprenavir (600 mg twice daily) and ritonavir (100 or 200 mg twice daily), no dosage adjustment is necessary. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.

Further, if efavirenz is given in combination with amprenavir and nelfinavir, no dosage adjustment is necessary for any of the medicinal products. Treatment with efavirenz in combination with amprenavir and saquinavir is not recommended, as the exposure to both PIs is expected to be significantly decreased. No dose recommendation can be given for the co-administration of amprenavir with another PI and efavirenz in children and patients with renal impairment. Such combinations should be avoided in patients with hepatic impairment.

Atazanavir: co-administration of efavirenz and atazanavir in combination with ritonavir may lead to increases in efavirenz exposure which may worsen the tolerability profile of efavirenz. Co-administration of efavirenz 600 mg with atazanavir in combination with low-dose ritonavir resulted in substantial decreases in atazanavir exposure, necessitating dosage adjustment of atazanavir (refer to the Summary of Product Characteristics for atazanavir).

Indinavir: when indinavir (800 mg every 8 hours) was given with efavirenz (200 mg every 24 hours), the indinavir AUC and C_{trough} were decreased by approximately 31 % and 40 % respectively. When indinavir at an increased dose (1,000 mg every 8 hours) was given with efavirenz (600 mg once daily) in uninfected volunteers, the indinavir AUC and C_{trough} were decreased on average by 33 - 46 % and 39 - 57 %, respectively (ranges represent diurnal variation), compared to when indinavir was given alone at the standard dose (800 mg every 8 hours). Similar differences in indinavir AUC and C_{trough} were also observed in HIV infected patients who received indinavir (1,000 mg every 8 hours) with efavirenz (600 mg once daily) compared to indinavir given alone (800 mg every 8 hours). While the clinical significance of decreased indinavir concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz and indinavir.

When efavirenz 600 mg once daily was given with indinavir/ritonavir 800/100 mg twice daily in uninfected volunteers (n = 14), the indinavir AUC, C_{min}, and C_{max} were decreased by approximately 25 %, 50 % and 17 %, respectively, compared to when indinavir/ritonavir 800/100 mg twice daily were given without efavirenz. The geometric mean C_{min} for indinavir (0.33 mg/l) when given with ritonavir and efavirenz was higher than the mean historical C_{min} (0.15 mg/l) when indinavir was given alone at 800 mg every 8 hours. The pharmacokinetics of efavirenz given in combination with indinavir/ritonavir were comparable to efavirenz alone (600 mg once daily).

When efavirenz 600 mg once daily was given with indinavir/ritonavir 800/100 mg twice daily in HIV-1 infected patients (n = 6), the pharmacokinetics of indinavir and efavirenz were generally comparable to these uninfected volunteer data.

No adjustment of the dose of efavirenz is necessary when given with indinavir or indinavir/ritonavir.
For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.

Lopinavir/ritonavir: when used in combination with efavirenz and two NRTIs, 533/133 mg lopinavir/ritonavir twice daily yielded similar lopinavir plasma concentrations as compared to lopinavir/ritonavir 400/100 mg twice daily without efavirenz (historical data). When co-administered with efavirenz, an increase of the lopinavir/ritonavir 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 dosage adjustment might be insufficient in some patients. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.

Nelfinavir: the AUC and C_{max} of nelfinavir are increased by 20 % and 21 %, respectively when given with efavirenz. The combination was generally well tolerated and no dose adjustment is necessary when nelfinavir is administered in combination with efavirenz.

Ritonavir: co-administration of efavirenz and ritonavir may lead to increases in efavirenz exposure. When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (for example, dizziness, nausea, paraesthesia and elevated liver enzymes occurred). Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available. When using efavirenz in a regimen including low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, namely due to possible pharmacodynamic interaction.

Saquinavir: when saquinavir (1,200 mg given 3 times a day, soft capsule formulation) was given with efavirenz, the saquinavir AUC and C_{max} were decreased by 62 % and 50 % respectively. Use of efavirenz in combination with saquinavir as the sole PI is not recommended.

Saquinavir/ritonavir: no data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir above.

NRTIs: studies of the interaction between efavirenz and the combination of zidovudine and lamivudine were performed in HIV infected patients. No clinically significant pharmacokinetic interactions were observed. Specific interaction studies have not been performed with efavirenz and other NRTIs. Clinically significant interactions would not be 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.

NNRTIs: no studies have been performed with efavirenz in combination with other NNRTIs and the potential for pharmacokinetic or pharmacodynamic interactions is

unknown.

Antimicrobial agents:

Rifamycins: rifampicin reduced efavirenz AUC by 26 % and C_{max} by 20 % in uninfected volunteers. The dose of efavirenz must be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with efavirenz. In one study in uninfected volunteers, efavirenz induced a reduction in rifabutin C_{max} and AUC by 32 % and 38 % respectively. Rifabutin had no significant effect on the pharmacokinetics of efavirenz. These data suggest that the daily dose of rifabutin should be increased by 50 % when administered with efavirenz and that the rifabutin dose may be doubled for regimens in which rifabutin is given two or three times a week in combination with efavirenz.

Macrolide antibiotics:

Azithromycin: co-administration of single doses of azithromycin and multiple doses of efavirenz in uninfected volunteers did not result in any clinically significant pharmacokinetic interaction. No dosage adjustment is necessary when azithromycin is given in combination with efavirenz.

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 efavirenz. The clinical significance of these changes in clarithromycin plasma levels is not known. 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 may be considered.

Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.

Antifungal agents:

Voriconazole: co-administration of efavirenz (400 mg orally once daily) with voriconazole (200 mg orally every 12 hours) in uninfected volunteers resulted in a 2-way interaction. The steady state AUC and C_{max} of voriconazole decreased by on average 77 % and 61 %, respectively, while the steady state AUC and C_{max} of efavirenz increased by on average 44 % and 38 %, respectively. Co-administration of efavirenz and voriconazole is contraindicated.

Itraconazole: co-administration of efavirenz (600 mg orally once daily) with itraconazole (200 mg orally every 12 hours) in uninfected volunteers decreased the steady state AUC, C_{max}, and C_{min} of itraconazole by 39 %, 37 %, and 44 %, respectively, and of hydroxyitraconazole by 37 %, 35 %, and 43 %, respectively, compared to itraconazole administered alone. The pharmacokinetics of efavirenz were

not affected. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Other antifungal agents: no clinically significant pharmacokinetic interactions were seen when fluconazole and efavirenz were co-administered to uninfected volunteers. The potential for interactions with efavirenz and other imidazole antifungals, such as ketoconazole, has not been studied.

Anticonvulsants:

Carbamazepine: co-administration of efavirenz (600 mg orally once daily) with carbamazepine (400 mg once daily) in uninfected volunteers resulted in a two-way interaction. The steady-state AUC, C_{max} and C_{min} of carbamazepine decreased by 27 %, 20 % and 35 %, respectively, while the steady-state AUC, C_{max} and C_{min} of efavirenz decreased by 36 %, 21 %, and 47 %, respectively. The steady-state AUC, C_{max} and C_{min} of the active carbamazepine epoxide metabolite remained unchanged. Carbamazepine plasma levels should be monitored periodically. There are no data with co-administration of higher doses of either medicinal product; therefore, no dose recommendation can be made, and alternative anticonvulsant treatment should be considered.

Other anticonvulsants: no data are available on the potential interactions of efavirenz with phenytoin, phenobarbital, or other anticonvulsants that are substrates of CYP450 isozymes. When efavirenz is administered concomitantly with these agents, there is a potential for reduction or increase in the plasma concentrations of each agent; therefore, periodic monitoring of plasma levels should be conducted. Specific interaction studies have not been performed with efavirenz and vigabatrin or gabapentin. Clinically significant interactions would not be expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and would be unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.

Lipid-lowering agents:

Co-administration of efavirenz with the HMG-CoA reductase inhibitors atorvastatin, pravastatin, or simvastatin has been shown to reduce the plasma concentration of the statin in uninfected volunteers. Cholesterol levels should be periodically monitored. Dosage adjustments of statins may be required (refer to the Summary of Product Characteristics for the statin).

Atorvastatin: co-administration of efavirenz (600 mg orally once daily) with atorvastatin (10 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of atorvastatin by 43 % and 12 %, respectively, of 2-hydroxy atorvastatin by 35 % and 13 %, respectively, of 4-hydroxy atorvastatin by 4 % and 47 %, respectively, and of total active HMG-CoA reductase inhibitors by 34 % and 20 %, respectively, compared to atorvastatin administered alone.

Pravastatin: co-administration of efavirenz (600 mg orally once daily) with pravastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and

C_{max} of pravastatin by 40 % and 18 %, respectively, compared to pravastatin administered alone.

Simvastatin: co-administration of efavirenz (600 mg orally once daily) with simvastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of simvastatin by 69 % and 76 %, respectively, of simvastatin acid by 58 % and 51 %, respectively, of total active HMG-CoA reductase inhibitors by 60 % and 62 %, respectively, and of total HMG-CoA reductase inhibitors by 60 % and 70 %, respectively, compared to simvastatin administered alone.

Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values. No dosage adjustment is necessary for efavirenz.

Other interactions:

Antacids/famotidine: neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz in uninfected volunteers. These data suggest that alteration of gastric pH by other medicinal products would not be expected to affect efavirenz absorption.

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 efavirenz. 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 efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

Methadone: in a study of HIV infected IV drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

St. John's wort *(Hypericum perforatum)*: plasma levels of efavirenz can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum)*. This is due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort. Herbal preparations containing St. John's wort must not be used concomitantly with efavirenz. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort and the dose of efavirenz may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment.

Antidepressants: there were no clinically significant effects on pharmacokinetic parameters when paroxetine and efavirenz were co-administered. No dose adjustments are necessary for either efavirenz or paroxetine when these medicinal products are co-administered. Since fluoxetine shares a similar metabolic profile with paroxetine,

i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine. Sertraline, a CYP3A4 substrate, did not significantly alter the pharmacokinetics of efavirenz. Efavirenz decreased sertraline C_{max}, C_{24} and AUC by 28.6 to 46.3 %. Sertraline dose increases should be guided by clinical response.

Cetirizine: the H1-antihistamine, cetirizine, had no clinically significant effect on efavirenz pharmacokinetic parameters. Efavirenz decreased cetirizine C_{max} by 24 % but did not alter cetirizine AUC. These changes are not considered to be clinically significant. No dose adjustments are necessary for either efavirenz or cetirizine when these medicinal products are co-administered.

Lorazepam: efavirenz increased lorazepam C_{max} and AUC by 16.3 % and 7.3 % respectively. These changes are not considered to be clinically significant. No dose adjustments are necessary for either efavirenz or lorazepam when these medicinal products are co-administered.

Calcium channel blockers: co-administration of efavirenz (600 mg orally once daily) with diltiazem (240 mg orally once daily) in uninfected volunteers decreased the steady state AUC, Cmax , and Cmin of diltiazem by 69%, 60%, and 63%, respectively; desacetyl diltiazem by 75%, 64%, and 62%, respectively; and N monodesmethyl diltiazem by 37%, 28%, and 37%, respectively, compared to diltiazem administered alone. Diltiazem dose adjustments should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem).

Although the pharmacokinetic parameters of efavirenz were slightly increased (11%-16%), these changes are not considered clinically significant and, thus, no dosage adjustment is necessary for efavirenz when administered with diltiazem.

No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme (eg, verapamil, felodipine, nifedipine, nicardipine). When efavirenz is administered concomitantly with one of these agents, there is a potential for reduction in the plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker).

Pregnancy and lactation

Pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. Efavirenz should not be used during pregnancy unless there are no other appropriate treatment options.

There are no adequate and well-controlled studies of efavirenz in pregnant women. In post-marketing experience through an antiretroviral pregnancy registry, more than 200 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been reported with no specific malformation pattern.

Retrospectively in this registry, a small number of cases of neural tube defects, including meningomyelocele, have been reported but causality has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects.

Studies in rats have demonstrated that efavirenz is excreted in milk reaching concentrations much higher than those in maternal plasma. It is not known whether efavirenz is excreted in human milk. Since animal data suggest that the substance may be passed into breast milk, it is recommended that mothers taking efavirenz do not breast feed their infants. It is recommended that HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.

Adverse effects

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported treatment-related undesirable effects of at least moderate severity reported in at least 5 % of patients were rash (11.6 %), dizziness (8.5 %), nausea (8.0 %), headache (5.7 %) and fatigue (5.5 %). The most notable undesirable effects associated with efavirenz are rash and nervous system symptoms. The administration of efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of undesirable effects.

The long-term safety profile of efavirenz-containing regimens was evaluated in a controlled trial (006) in which patients received efavirenz + zidovudine + lamivudine (n = 412, median duration 180 weeks), efavirenz + indinavir (n = 415, median duration 102 weeks), or indinavir + zidovudine + lamivudine (n = 401, median duration 76 weeks). Long-term use of efavirenz in this study was not associated with any new safety concerns.

Rash: in clinical studies, 26 % of patients treated with 600 mg of efavirenz experienced skin rash compared with 17 % of patients treated in control groups. Skin rash was considered treatment related in 18 % of patients treated with efavirenz. Severe rash occurred in less than 1 % of patients treated with efavirenz, and 1.7 % discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1 %.

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with efavirenz. In most patients rash resolves with continuing therapy with efavirenz within one month. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when efavirenz is restarted.

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz, and two discontinued because of rash.

Psychiatric symptoms: serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1,008 patients treated with regimens containing efavirenz for an average of 1.6 years and 635 patients treated with control regimens for an average of 1.3 years, the frequency of specific serious psychiatric events are detailed hereafter:

	Efavirenz regimen	Control regimen
- severe depression	1.6 %	0.6 %
- suicidal ideation	0.6 %	0.3 %
- non-fatal suicide attempts	0.4 %	0 %
- aggressive behaviour	0.4 %	0.3 %
- paranoid reactions	0.4 %	0.3 %
- manic reactions	0.1 %	0 %

Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences with the frequency of each of the above events ranging from 0.3 % for manic reactions to 2.0 % for both severe depression and suicidal ideation. There have also been post-marketing reports of death by suicide, delusions and psychosis-like behaviour.

Nervous system symptoms: in clinical controlled trials, frequently reported undesirable effects in patients receiving 600 mg efavirenz with other antiretroviral agents included, but were not limited to: dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms of moderate-to-severe intensity were experienced by 19.4 % of patients compared to 9.0 % of patients receiving control regimens. These symptoms were severe in 2.0 % of patients receiving efavirenz 600 mg daily and in 1.3 % of patients receiving control regimens. In clinical studies 2.1 % of patients treated with 600 mg of efavirenz discontinued therapy because of nervous system symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. In one clinical study, the monthly prevalence of nervous system symptoms of at least moderate severity between weeks 4 and 48, ranged from 5 % - 9 % in patients treated with regimens containing efavirenz and 3 % - 5 % in patients treated with the control regimen. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Nervous system symptoms may occur more frequently when efavirenz is taken concomitantly with meals possibly due to increased efavirenz plasma levels. Dosing at bedtime seems to improve the tolerability of these symptoms and can be recommended during the first weeks of therapy and in patients who continue to experience these symptoms. Dose reduction or splitting the daily dose has not been shown to provide benefit.

Analysis of long-term data from study 006 (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with efavirenz + zidovudine + lamivudine, efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system

symptoms among efavirenz-treated patients were generally similar to those in the control arm.

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below. Frequency is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000) including isolated reports.

Immune system disorders
uncommon: hypersensitivity

Psychiatric disorders
common: anxiety, depression
uncommon: affect lability, aggression, euphoric mood, hallucination, mania, paranoia, suicide attempt, suicide ideation

Nervous system disorders
common: abnormal dreams, disturbance in attention, dizziness, headache, insomnia, somnolence
uncommon: agitation, amnesia, ataxia, coordination abnormal, confusional state, convulsions, thinking abnormal

Eye disorders
uncommon: vision blurred

Ear and labyrinth disorders
uncommon: vertigo

Gastrointestinal disorders
common: abdominal pain, diarrhoea, nausea, vomiting
uncommon: pancreatitis acute

Hepatobiliary disorders
uncommon: hepatitis acute

Skin and subcutaneous tissue disorders
very common: rash
common: pruritus
uncommon: erythema multiforme

General disorders and administration site conditions
common: fatigue

Immune Reactivation Syndrome: in HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Laboratory test abnormalities:

Liver enzymes: elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to greater than five times the upper limit of the normal range (ULN) were seen in 3 % of 1,008 patients treated with 600 mg of efavirenz (5 - 8 % after long-term treatment in study 006). Similar elevations were seen in patients treated with control regimens (5 % after long-term treatment). Elevations of gamma-glutamyltransferase (GGT) to greater than five times ULN were observed in 4 % of all patients treated with 600 mg of efavirenz and 1.5 - 2 % of patients treated with control regimens (7 % of efavirenz-treated patients and 3 % of control-treated patients after long-term treatment). Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction. In the long-term study (006), 1 % of patients in each treatment arm discontinued because of liver or biliary system disorders.

In the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, elevations in AST to greater than five times ULN developed in 13 % of patients in the efavirenz arms and 7 % of those in the control arm, and elevations in ALT to greater than five times ULN developed in 20 % of patients in the efavirenz arms and 7 % of the patients in the control arm. Among co-infected patients, 3 % of those treated with efavirenz-containing regimens and 2 % in the control arm discontinued from the study because of liver or biliary system disorders. Reasons for discontinuation among co-infected recipients of efavirenz included abnormalities in hepatic enzymes; there were no discontinuations reported in this study for cholestatic hepatitis, hepatic failure, or fatty liver.

Amylase: in the clinical trial subset of 1,008 patients, asymptomatic increases in serum amylase levels greater than 1.5 times the upper limit of normal were seen in 10 % of patients treated with efavirenz and 6 % of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown.

Lipids: increases in total cholesterol of 10 - 20 % have been observed in some uninfected volunteers receiving efavirenz. In clinical trials of various efavirenz-containing regimens in treatment naive patients, total cholesterol, HDL-cholesterol, and triglycerides increased over 48 weeks of treatment (21 – 31 %, 23 – 34 %, and 23 – 49 %, respectively). The proportion of patients with a total cholesterol/HDL-cholesterol ratio greater than 5 was unchanged. The magnitude of changes in lipid

levels may be influenced by factors such as duration of therapy and other components of the antiretroviral regimen.

Cannabinoid test interaction: efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz. False positive test results have only been observed with the CEDIA DAU Multi-Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

Post-marketing experience with efavirenz has shown the following additional adverse events to occur in association with efavirenz-containing antiretroviral treatment regimens: delusion, gynaecomastia, hepatic failure, neurosis, photoallergic dermatitis, psychosis and completed suicide.

Adolescents and children: undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (in a clinical study including 57 children who received efavirenz during a 48-week period, rash was reported in 46 %) and was more often of higher grade than in adults (severe rash was reported in 5.3 % of children). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered. Although nervous system symptoms are difficult for young children to report, they appear to be less frequent in children and were generally mild. In the study of 57 children, 3.5 % of patients experienced nervous system symptoms of moderate intensity, predominantly dizziness. No child had severe symptoms or had to discontinue because of nervous system symptoms.

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