

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz Teva 600 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg efavirenz.

Excipients, with known effect: each film-coated tablet contains 10.5 mg lactose monohydrate (equivalent to 9.98 mg lactose anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Yellow, capsule-shaped, film-coated tablet debossed with “Teva” on one side and “7541” on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efavirenz is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 years of age and older.

Efavirenz has not been adequately studied in patients with advanced HIV disease, namely in patients with CD₄ counts < 50 cells/mm³, or after failure of protease inhibitor (PI)-containing regimens. Although cross-resistance of efavirenz with PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI-based combination therapy after failure of regimens containing efavirenz.

For a summary of clinical and pharmacodynamic information, see section 5.1.

4.2 Posology and method of administration

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

Posology

Efavirenz must be given in combination with other antiretroviral medicines (see section 4.5).

In order to improve the tolerability of nervous system adverse reactions, bedtime dosing is recommended (see section 4.8).

Adults and adolescents over 40 kg

The recommended dose of efavirenz in combination with nucleoside analogue reverse transcriptase inhibitors (NRTIs) with or without a PI (see section 4.5) is 600 mg orally, once daily.

Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg. Efavirenz hard capsules are available for these patients.

Dose adjustment

If efavirenz is co-administered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the efavirenz dose must be reduced by 50%, *i.e.* to 300 mg once daily. When treatment with voriconazole is stopped, the initial dose of efavirenz should be restored (see section 4.5).

If efavirenz is co-administered with rifampicin to patients weighing 50 kg or more, an increase in the dose of efavirenz to 800 mg/day may be considered (see section 4.5).

Special populations

Renal impairment

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 (see section 4.4).

Hepatic impairment

Patients with mild liver disease may be treated with their normally recommended dose of efavirenz. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms (see sections 4.3 and 4.4).

Method of Administration

It is recommended that efavirenz be taken on an empty stomach. The increased efavirenz concentrations observed following administration with food may lead to an increase in frequency of adverse reactions (see sections 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with severe hepatic impairment (Child Pugh Class C) (see section 5.2).

Co-administration 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 adverse reactions [for example, cardiac arrhythmias, prolonged sedation or respiratory depression] (see section 4.5).

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 (see section 4.5).

4.4 Special 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 (see section 5.1).

Co-administration of efavirenz with the fixed-combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate is not recommended, unless needed for dose adjustment (for example, with rifampicin).

Concomitant use of *Ginkgo biloba* extract is not recommended (see section 4.5).

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

While effective viral suppression with antiretroviral therapy, has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 (see section 4.8). Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited (see section 4.8). Efavirenz is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking another NNRTI.

Psychiatric symptoms

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see section 4.8).

Nervous system symptoms

Symptoms including, but not limited to dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported adverse reactions in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). 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 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 (see section 4.5). Caution must be taken in any patient with a history of seizures.

Hepatic events

A few of the post-marketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (see section 4.8). Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.

Effect of food

The administration of Efavirenz Teva with food may increase efavirenz exposure (see section 5.2) and may lead to an increase in the frequency of adverse reactions (see section 4.8). It is recommended that Efavirenz Teva 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 pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution 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 (see section 4.8).

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Special populations

Liver disease

Efavirenz is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2) and not recommended in patients with moderate hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild hepatic impairment. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see section 4.2).

The safety and efficacy of efavirenz has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse reactions. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. 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 (see section 4.8).

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 (see section 4.2). There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

Older patients

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

Paediatric population

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.

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.

Lactose

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.

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz is an in vivo inducer of CYP3A4, CYP2B6 and UGT1A1. Compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with efavirenz. In vitro efavirenz is also an inhibitor of CYP3A4. Theoretically, efavirenz may therefore initially increase the exposure to CYP3A4 substrates and caution is warranted for CYP3A4 substrates with narrow therapeutic index (see section 4.3). Efavirenz may be an inducer of CYP2C19 and CYP2C9; however inhibition has also been observed in vitro and the net effect of co-administration with substrates of these enzymes is not clear (see section 5.2).

Efavirenz exposure may be increased when given with medicinal products (for example, ritonavir) or food (for example, grapefruit juice), which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example *Ginkgo biloba* extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated (see section 4.3). Concomitant use of *Ginkgo biloba* extracts is not recommended (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

Contraindications of concomitant use

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 (see section 4.3).

St. John's wort (Hypericum perforatum)

Co-administration of efavirenz and St. John's wort or herbal preparations containing St. John's wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John's wort due to induction of drug-metabolising enzymes and/or transport proteins by St. John's wort. 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 (see section 4.3).

Other interactions

Interactions between efavirenz and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in Table 1 below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, and once every 8 or 12 hours as “q8h” or “q12h”). If available, 90% or 95% confidence intervals are shown in parentheses. Studies were conducted in healthy subjects unless otherwise noted.

Table 1: Interactions between efavirenz and other medicinal products in adults

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C _{max} , C _{min} with confidence intervals if available ^a (mechanism)	Recommendation concerning co-administration with efavirenz
ANTI-INFECTIVES		
HIV antivirals		
Protease inhibitors (PI)		
Atazanavir/ritonavir/efavirenz (400 mg once daily/100 mg once daily/600 mg once daily, all administered with food)	Atazanavir (pm): AUC: ↔* (↓ 9 to ↑ 10) C _{max} : ↑ 17%* (↑ 8 to ↑ 27) C _{min} : ↓ 42%* (↓ 31 to ↓ 51)	Co-administration of efavirenz with atazanavir/ritonavir is not recommended. If the co-administration of atazanavir with an NNRTI is required, an increase in the dose of both atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close clinical monitoring.
Atazanavir/ritonavir/efavirenz (400 mg once daily/200 mg once daily/600 mg once daily, all administered with food)	Atazanavir (pm): AUC: ↔*/** (↓ 10 to ↑ 26) C _{max} : ↔*/** (↓ 5 to ↑ 26) C _{min} : ↑ 12%*/** (↓ 16 to ↑ 49) (CYP3A4 induction) * When compared to atazanavir 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C _{min} might negatively impact the efficacy of atazanavir. ** Based on historical comparison	

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C _{max} , C _{min} with confidence intervals if available ^a (mechanism)	Recommendation concerning co-administration with efavirenz
Darunavir/ritonavir/efavirenz (300 mg twice daily*/100 mg twice daily/600 mg once daily) *lower than recommended doses, similar findings are expected with recommended doses	Darunavir: AUC: ↓ 13% C _{min} : ↓ 31% C _{max} : ↓ 15% (CYP3A4 induction) Efavirenz: AUC: ↑ 21% C _{min} : ↑ 17% C _{max} : ↑ 15% (CYP3A4 inhibition)	Efavirenz in combination with darunavir/ritonavir 800/100 mg once daily may result in suboptimal darunavir C _{min} . If efavirenz is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. This combination should be used with caution. See also ritonavir row below.
Fosamprenavir/ritonavir/efavirenz (700 mg twice daily/100 mg twice daily/600 mg once daily)	No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for any of these medicinal products. See also ritonavir row below.
Fosamprenavir/nelfinavir/efavirenz Fosamprenavir/saquinavir/efavirenz	Interaction not studied Interaction not studied	No dose adjustment is necessary for any of these medicinal products. Not recommended as the exposure to both PIs is expected to be significantly decreased.
Indinavir/efavirenz (800 mg q8h/200 mg once daily)	Indinavir: AUC: ↓ 31% (↓ 8 to ↓47) C _{min} : ↓ 40% A similar reduction in indinavir exposures was observed when indinavir 1000 mg q8h was given with efavirenz 600 mg daily. (CYP3A4 induction) Efavirenz: No clinically significant pharmacokinetic interaction	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. No dose adjustment is necessary for efavirenz when given with indinavir or indinavir/ritonavir.
Indinavir/ritonavir/efavirenz (800 mg twice daily/100 mg twice daily/600 mg once daily)	Indinavir: AUC: ↓ 25% (↓ 16 to ↓32) ^b C _{max} : ↓ 17% (↓ 6 to ↓ 26) ^b C _{min} : ↓ 50% (↓ 40 to ↓ 59) ^b Efavirenz: No clinically significant pharmacokinetic interaction 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 q8h. In HIV-1 infected patients (n=6), the pharmacokinetics of indinavir and efavirenz were generally comparable to these uninfected volunteer data.	See also ritonavir row below.
Lopinavir/ritonavir soft capsules or oral solution/efavirenz Lopinavir/ritonavir tablets/efavirenz	Substantial decrease in lopinavir exposure.	With efavirenz, an increase of the lopinavir/ritonavir soft capsule or oral solution doses by 33% should be considered (4 capsules/ ~6.5 ml twice daily instead of 3

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
(400/100 mg twice daily/ 600 mg once daily) (500/125 mg twice daily/ 600 mg once daily)	Lopinavir concentrations: ↓ 30-40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz	capsules/5 ml twice daily). Caution is warranted since this dose adjustment might be insufficient in some patients. The dose of lopinavir/ritonavir tablets should be increased to 500/125 mg twice daily when co-administered with efavirenz 600 mg once daily. See also ritonavir row below.
Nelfinavir/efavirenz (750 mg q8h/600 mg once daily)	Nelfinavir: AUC: ↑ 20% (↑ 8 to ↑ 34) C _{max} : ↑ 21% (↑ 10 to ↑ 33) The combination was generally well tolerated.	No dose adjustment is necessary for either medicinal product.
Ritonavir/efavirenz (500 mg twice daily/600 mg once daily)	Ritonavir: Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔ Morning C _{max} : ↑ 24% (↑ 12 to ↑ 38) Evening C _{max} : ↔ Morning C _{min} : ↑ 42% (↑ 9 to ↑ 86) ^b Evening C _{min} : ↑ 24% (↑ 3 to ↑ 50) ^b Efavirenz: AUC: ↑ 21% (↑ 10 to ↑ 34) C _{max} : ↑ 14% (↑ 4 to ↑ 26) C _{min} : ↑ 25% (↑ 7 to ↑ 46) ^b (Inhibition of CYP-mediated oxidative metabolism) 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 with low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction.
Saquinavir/ritonavir/efavirenz	Interaction not studied	No data are available to make a dose recommendation. See also ritonavir row above. Use of efavirenz in combination with saquinavir as the sole protease inhibitor is not recommended.
CCR5 antagonist		
Maraviroc/efavirenz (100 mg twice daily/600 mg once daily)	Maraviroc: AUC ₁₂ : ↓ 45% (↓ 38 to ↓ 51) C _{max} : ↓ 51% (↓ 37 to ↓ 62) Efavirenz concentrations not measured, no effect is expected.	Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc.
Integrase strand transfer inhibitor		
Raltegravir/efavirenz (400 mg single dose/ -)	Raltegravir: AUC: ↓ 36% C ₁₂ : ↓ 21% C _{max} : ↓ 36% (UGT1A1 induction)	No dose adjustment is necessary for raltegravir.

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
NRTIs and NNRTIs		
NRTIs/efavirenz	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine and tenofovir disoproxil fumarate. Clinically significant interactions are not expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.	No dose adjustment is necessary for either medicinal product.
NNRTIs/efavirenz	Interaction not studied	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of efavirenz and another NNRTI is not recommended.
Hepatitis C antivirals		
Boceprevir/Efavirenz (800 mg 3 times daily/600 mg once daily)	<p>Boceprevir: AUC: ↔ 19%* C_{max}: ↔ 8% C_{min}: ↓ 44%</p> <p>Efavirenz: AUC: ↔ 20% C_{max}: ↔ 11% (CYP3A induction - effect on boceprevir) *0-8 hours</p> <p>No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of ≤25%</p>	Plasma trough concentrations of boceprevir were decreased when administered with efavirenz. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.
Telaprevir/Efavirenz (1,125 mg q8h/600 mg once daily)	<p>Telaprevir (relative to 750 mg q8h): AUC: ↓ 18% (↓ 8 to ↓ 27) C_{max}: ↓ 14% (↓ 3 to ↓ 24) C_{min}: ↓ 25% (↓ 14 to ↓ 34)%</p> <p>Efavirenz: AUC: ↓ 18% (↓ 10 to ↓ 26) C_{max}: ↓ 24% (↓ 15 to ↓ 32) C_{min}: ↓ 10% (↑ 1 to ↓ 19%) (CYP3A induction by efavirenz)</p>	If efavirenz and telaprevir are co-administered, telaprevir 1,125 mg every 8 hours should be used.
Simeprevir/Efavirenz (150 mg once daily /600 mg once daily)	<p>Simeprevir: AUC: ↓ 71% (↓ 67 to ↓ 74) C_{max}: ↓ 51% (↓ 46 to ↓ 56) C_{min}: ↓ 91% (↓ 88 to ↓ 92)</p> <p>Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔</p> <p>No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of</p>	Concomitant administration of simeprevir with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of simeprevir. Co-administration of simeprevir with efavirenz is not recommended.

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
	≤25% (CYP3A4 enzyme induction)	
Antibiotics		
Azithromycin/efavirenz (600 mg single dose/400 mg once daily)	No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for either medicinal product.
Clarithromycin/efavirenz (500 mg q12h/400 mg once daily)	Clarithromycin: AUC: ↓ 39% (↓ 30 to ↓ 46) C _{max} : ↓ 26% (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34% (↑ 18 to ↑ 53) C _{max} : ↑ 49% (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ C _{max} : ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin.	The clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered. No dose adjustment is necessary for efavirenz.
Other macrolide antibiotics (e.g. erythromycin)/efavirenz	Interaction not studied	No data are available to make a dose recommendation.
Antimycobacterials		
Rifabutin/efavirenz (300 mg once daily/600 mg once daily)	Rifabutin: AUC: ↓ 38% (↓ 28 to ↓ 47) C _{max} : ↓ 32% (↓ 15 to ↓ 46) C _{min} : ↓ 45% (↓ 31 to ↓ 56) Efavirenz: AUC: ↔ C _{max} : ↔ C _{min} : ↓ 12% (↓ 24% to ↑ 1%) (CYP3A4 induction)	The daily dose of rifabutin should be increased by 50% when administered with efavirenz. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with efavirenz. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2).
Rifampicin/efavirenz (600 mg once daily/600 mg once daily)	Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) C _{max} : ↓ 20% (↓ 11 to ↓ 28) C _{min} : ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)	When taken with rifampicin in patients weighing 50 kg or greater, increasing efavirenz daily dose to 800 mg may provide exposure similar to a daily dose of 600 mg when taken without rifampicin. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2). No dose adjustment is necessary for rifampicin.
Antifungals		
Itraconazole/efavirenz (200 mg q12h/600 mg once daily)	Itraconazole: AUC: ↓ 39% (↓ 21 to ↓ 53)	Since no dose recommendation for itraconazole can be made,

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
	C _{max} : ↓ 37% (↓ 20 to ↓ 51) C _{min} : ↓ 44% (↓ 27 to ↓ 58) (Decrease in itraconazole concentrations: CYP3A4 induction) Hydroxyitraconazole: AUC: ↓ 37% (↓ 14 to ↓ 55) C _{max} : ↓ 35% (↓ 12 to ↓ 52) C _{min} : ↓ 43% (↓ 18 to ↓ 60) Efavirenz: No clinically significant pharmacokinetic change.	alternative antifungal treatment should be considered.
Posaconazole/efavirenz (–/400 mg once daily)	Posaconazole: AUC: ↓ 50% C _{max} : ↓ 45% (UDP-G induction)	Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.
Voriconazole/efavirenz (200 mg twice daily/400 mg once daily)	Voriconazole: AUC: ↓ 77% C _{max} : ↓ 61% Efavirenz: AUC: ↑ 44% C _{max} : ↑ 38%	When efavirenz is co-administered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg twice daily and the efavirenz dose must be reduced by 50%, <i>i.e.</i> to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored.
Voriconazole/efavirenz (400 mg twice daily/300 mg once daily)	Voriconazole: AUC: ↓ 7% (↓ 23 to ↑ 13) * C _{max} : ↑ 23% (↓ 1 to ↑ 53) * Efavirenz: AUC: ↑ 17% (↑ 6 to ↑ 29) ** C _{max} : ↔** *compared to 200 mg twice daily alone ** compared to 600 mg once daily alone (Competitive inhibition of oxidative metabolism)	
Fluconazole/efavirenz (200 mg once daily/400 mg once daily)	No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for either medicinal product.
Ketoconazole and other imidazole antifungals	Interaction not studied	No data are available to make a dose recommendation.
Antimalarials		
Artemether/lumefantrine/ Efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600mg once daily)	Artemether: AUC: ↓ 51% C _{max} : ↓ 21% Dihydroartemisinin: AUC: ↓ 46% C _{max} : ↓ 38% Lumefantrine: AUC: ↓ 21% C _{max} : ↔ Efavirenz: AUC: ↓ 17%	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when efavirenz and artemether/lumefantrine tablets are coadministered.

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
	C _{max} : ↔ (CYP3A4 induction)	
Atovaquone and proguanil hydrochloride/Efavirenz (250/100 mg single dose/600 mg once daily)	Atovaquone: AUC: ↓ 75% (↓ 62 to ↓ 84) C _{max} : ↓ 44% (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43% (↓ 7 to ↓ 65) C _{max} : ↔	Concomitant administration of atovaquone/proguanil with efavirenz should be avoided whenever possible.
ACID-REDUCING AGENTS		
Aluminium hydroxide-magnesium hydroxide-simethicone antacid/efavirenz (30 ml single dose/400 mg single dose)	Neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz.	Co-administration of efavirenz with medicinal products that alter gastric pH would not be expected to affect efavirenz absorption.
Famotidine/efavirenz (40 mg single dose/400 mg single dose)		
ANTIANXIETY AGENTS		
Lorazepam/efavirenz (2 mg single dose/600 mg once daily)	Lorazepam: AUC: ↑ 7% (↑ 1 to ↑ 14) C _{max} : ↑ 16% (↑ 2 to ↑ 32) These changes are not considered clinically significant.	No dose adjustment is necessary for either medicinal product.
ANTICOAGULANTS		
Warfarin/efavirenz Acenocoumarol/Efavirenz	Interaction not studied. Plasma concentrations and effects of warfarin or acenocoumarol are potentially increased or decreased by efavirenz.	Dose adjustment of warfarin or acenocoumarol may be required.
ANTICONVULSANTS		
Carbamazepine/efavirenz (400 mg once daily/600 mg once daily)	Carbamazepine: AUC: ↓ 27% (↓ 20 to ↓ 33) C _{max} : ↓ 20% (↓ 15 to ↓ 24) C _{min} : ↓ 35% (↓ 24 to ↓ 44) Efavirenz: AUC: ↓ 36% (↓ 32 to ↓ 40) C _{max} : ↓ 21% (↓ 15 to ↓ 26) C _{min} : ↓ 47% (↓ 41 to ↓ 53) (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction) The steady-state AUC, C _{max} and C _{min} of the active carbamazepine epoxide metabolite remained unchanged. Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.	No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.
Phenytoin, phenobarbital, and other anticonvulsants that are substrates of CYP450 isoenzymes	Interaction not studied. There is a potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other	When efavirenz is co-administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
	anticonvulsants that are substrates of CYP450 isoenzymes when co-administered with efavirenz.	monitoring of anticonvulsant levels should be conducted.
Valproic acid/efavirenz (250 mg twice daily/600 mg once daily)	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.	No dose adjustment is necessary for efavirenz. Patients should be monitored for seizure control.
Vigabatrin/efavirenz Gabapentin/efavirenz	Interaction not studied. Clinically significant interactions are not expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and are unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.	No dose adjustment is necessary for any of these medicinal products.
ANTIDEPRESSANTS		
Selective Serotonin Re-uptake Inhibitors (SSRIs)		
Sertraline/efavirenz (50 mg once daily/600 mg once daily)	Sertraline: AUC: ↓ 39% (↓ 27 to ↓ 50) C _{max} : ↓ 29% (↓ 15 to ↓ 40) C _{min} : ↓ 46% (↓ 31 to ↓ 58) Efavirenz: AUC: ↔ C _{max} : ↑ 11% (↑ 6 to ↑ 16) C _{min} : ↔ (CYP3A4 induction)	Sertraline dose increases should be guided by clinical response. No dose adjustment is necessary for efavirenz.
Paroxetine/efavirenz (20 mg once daily/600 mg once daily)	No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for either medicinal product.
Fluoxetine/efavirenz	Interaction not studied. Since fluoxetine shares a similar metabolic profile with paroxetine, <i>i.e.</i> a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine.	No dose adjustment is necessary for either medicinal product.
Norepinephrine and dopamine reuptake inhibitor		
Bupropion/Efavirenz [150 mg single dose (sustained release)/600 mg once daily]	Bupropion: AUC: ↓ 55% (↓ 48 to ↓ 62) C _{max} : ↓ 34% (↓ 21 to ↓ 47) Hydroxybupropion: AUC: ↔ C _{max} : ↑ 50% (↑ 20 to ↑ 80) (CYP2B6 induction)	Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
ANTIHISTAMINES		
Cetirizine/efavirenz (10 mg single dose/600 mg once daily)	Cetirizine: AUC: ↔ C _{max} : ↓ 24% (↓ 18 to ↓ 30) These changes are not considered clinically significant. Efavirenz: No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for either medicinal product.

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
CARDIOVASCULAR AGENTS		
Calcium Channel Blockers		
Diltiazem/efavirenz (240 mg once daily/600 mg once daily)	<p>Diltiazem: AUC: ↓ 69% (↓ 55 to ↓ 79) C_{max}: ↓ 60% (↓ 50 to ↓ 68) C_{min}: ↓ 63% (↓ 44 to ↓ 75)</p> <p>Desacetyl diltiazem: AUC: ↓ 75% (↓ 59 to ↓ 84) C_{max}: ↓ 64% (↓ 57 to ↓ 69) C_{min}: ↓ 62% (↓ 44 to ↓ 75)</p> <p>N-monodesmethyl diltiazem: AUC: ↓ 37% (↓ 17 to ↓ 52) C_{max}: ↓ 28% (↓ 7 to ↓ 44) C_{min}: ↓ 37% (↓ 17 to ↓ 52)</p> <p>Efavirenz: AUC: ↑ 11% (↑ 5 to ↑ 18) C_{max}: ↑ 16% (↑ 6 to ↑ 26) C_{min}: ↑ 13% (↑ 1 to ↑ 26) (CYP3A4 induction) The increase in efavirenz pharmacokinetic parameters is not considered clinically significant.</p>	Dose adjustments of diltiazem should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem). No dose adjustment is necessary for efavirenz.
Verapamil, felodipine, nifedipine and nicardipine	Interaction not studied. When efavirenz is co-administered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme, there is a potential for reduction in the plasma concentrations of the calcium channel blocker.	Dose adjustments of calcium channel blockers should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker).
LIPID-LOWERING MEDICINAL PRODUCTS		
HMG CoA Reductase Inhibitors		
Atorvastatin/efavirenz (10 mg once daily/600 mg once daily)	<p>Atorvastatin: AUC: ↓ 43% (↓ 34 to ↓ 50) C_{max}: ↓ 12% (↓ 1 to ↓ 26)</p> <p>2-hydroxy atorvastatin: AUC: ↓ 35% (↓ 13 to ↓ 40) C_{max}: ↓ 13% (↓ 0 to ↓ 23)</p> <p>4-hydroxy atorvastatin: AUC: ↓ 4% (↓ 0 to ↓ 31) C_{max}: ↓ 47% (↓ 9 to ↓ 51)</p> <p>Total active HMG CoA reductase inhibitors: AUC: ↓ 34% (↓ 21 to ↓ 41) C_{max}: ↓ 20% (↓ 2 to ↓ 26)</p>	Cholesterol levels should be periodically monitored. Dose adjustment of atorvastatin may be required (refer to the Summary of Product Characteristics for atorvastatin). No dose adjustment is necessary for efavirenz.
Pravastatin/efavirenz (40 mg once daily/600 mg once daily)	Pravastatin: AUC: ↓ 40% (↓ 26 to ↓ 57) C _{max} : ↓ 18% (↓ 59 to ↑ 12)	Cholesterol levels should be periodically monitored. Dose adjustment of pravastatin may be required (refer to the Summary of Product Characteristics for pravastatin). No dose adjustment is necessary for efavirenz.

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
Simvastatin/efavirenz (40 mg once daily/600 mg once daily)	<p>Simvastatin: AUC: ↓ 69% (↓ 62 to ↓ 73) C_{max}: ↓ 76% (↓ 63 to ↓ 79)</p> <p>Simvastatin acid: AUC: ↓ 58% (↓ 39 to ↓ 68) C_{max}: ↓ 51% (↓ 32 to ↓ 58)</p> <p>Total active HMG Co-A reductase inhibitors: AUC: ↓ 60% (↓ 52 to ↓ 68) C_{max}: ↓ 62% (↓ 55 to ↓ 78)</p> <p>(CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values.</p>	Cholesterol levels should be periodically monitored. Dose adjustment of simvastatin may be required (refer to the Summary of Product Characteristics for simvastatin). No dose adjustment is necessary for efavirenz.
Rosuvastatin/efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces, therefore interaction with efavirenz is not expected.	No dose adjustment is necessary for either medicinal product.
HORMONAL CONTRACEPTIVES		
Oral: Ethinylestradiol + norgestimate / efavirenz (0.035 mg + 0.25 mg once daily/600 mg once daily)	<p>Ethinylestradiol: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 8% (↑ 14 to ↓ 25)</p> <p>Norelgestromin (active metabolite): AUC: ↓ 64% (↓ 62 to ↓ 67) C_{max}: ↓ 46% (↓ 39 to ↓ 52) C_{min}: ↓ 82% (↓ 79 to ↓ 85)</p> <p>Levonorgestrel (active metabolite): AUC: ↓ 83% (↓ 79 to ↓ 87) C_{max}: ↓ 80% (↓ 77 to ↓ 83) C_{min}: ↓ 86% (↓ 80 to ↓ 90) (induction of metabolism)</p> <p>Efavirenz: no clinically significant interaction. The clinical significance of these effects is not known.</p>	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
Injection: Depomedroxyprogesterone acetate (DMPA)/efavirenz (150 mg IM single dose DMPA)	In a 3-month drug interaction study, no significant differences in MPA pharmacokinetic parameters were found between subjects receiving efavirenz-containing antiretroviral therapy and subjects receiving no antiretroviral therapy. Similar results were found by other investigators, although the MPA plasma levels were more variable in the second study. In both studies, plasma progesterone levels for subjects receiving efavirenz and DMPA remained low consistent with suppression of ovulation.	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available^a (mechanism)	Recommendation concerning co-administration with efavirenz
Implant: Etonogestrel/efavirenz	Interaction not studied. Decreased exposure of etonogestrel may be expected (CYP3A4 induction). There have been occasional post-marketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
IMMUNOSUPPRESSANTS		
Immunosuppressants metabolized by CYP3A4 (e.g. ciclosporin, tacrolimus, sirolimus)/efavirenz	Interaction not studied. Decreased exposure of the immunosuppressant may be expected (CYP3A4 induction). These immunosuppressants are not anticipated to affect exposure of efavirenz.	Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.
OPIOIDS		
Methadone/efavirenz (stable maintenance, 35-100 mg once daily/600 mg once daily)	Methadone: AUC: ↓ 52% (↓ 33 to ↓ 66) C _{max} : ↓ 45% (↓ 25 to ↓ 59) (CYP3A4 induction) In a study of HIV infected intravenous 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.
Buprenorphine/naloxone/efavirenz	Buprenorphine: AUC: ↓ 50% Norbuprenorphine: AUC: ↓ 71% Efavirenz: No clinically significant pharmacokinetic interaction	Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine or efavirenz may not be necessary when co-administered.

^a 90% confidence intervals unless otherwise noted.

^b 95% confidence intervals.

Other interactions: efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV-infected subjects receiving efavirenz. Confirmatory testing by a more specific method such as gas chromatography/mass spectrometry is recommended in such cases.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

See below and section 5.3. Efavirenz should not be used during pregnancy, unless the patient's clinical condition requires such treatment. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.

Contraception in males and females

Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives, see section 4.5). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended.

Pregnancy

Efavirenz should not be used-during pregnancy, unless the patient's clinical condition requires such treatment. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz (see section 5.3).

There have been seven retrospective reports of findings consistent with neural tube defects, including meningocele, all in mothers exposed to efavirenz-containing regimens (excluding any efavirenz-containing fixed-dose combination tablets) in the first trimester. Two additional cases (1 prospective and 1 retrospective) including events consistent with neural tube defects have been reported with the fixed-dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate. A causal relationship of these events to the use of efavirenz has not been established, and the denominator is unknown. As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes are sealed), this potential risk would concern women exposed to efavirenz during the first trimester of pregnancy.

As of July 2013, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 904 pregnancies with first trimester exposure to efavirenz-containing regimens, resulting in 766 live births. One child was reported to have a neural tube defect, and the frequency and pattern of other birth defects were similar to those seen in children exposed to non-efavirenz-containing regimens, as well as those in HIV negative controls. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births.

Malformations have been observed in foetuses from efavirenz-treated monkeys (see section 5.3).

Breast-feeding

Efavirenz has been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz in newborns/infants. Risk to the infant cannot be excluded. Breast-feeding should be discontinued during treatment with efavirenz. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

The effect of efavirenz on male and female fertility in rats has only been evaluated at doses that achieved systemic drug exposures equivalent to or below those achieved in humans given recommended doses of efavirenz. In these studies, efavirenz did not impair mating or fertility of male or female rats (doses up to 100 mg/kg/bid), and did not affect sperm or offspring of treated male rats (doses up to 200 mg/bid). The reproductive performance of offspring born to female rats given efavirenz was not affected.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

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 adverse reactions 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 adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2–4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme, psychiatric adverse reactions including severe depression, death by suicide, and psychosis-like behaviour, and seizures have been reported in patients treated with efavirenz. The administration of efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

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.

b. Tabulated list of adverse reactions

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. Also listed in italics are adverse reactions observed post-marketing in association with efavirenz-containing antiretroviral treatment regimens. Frequency is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); or very rare ($< 1/10,000$).

<i>Immune system disorders</i>	
Uncommon	Hypersensitivity
<i>Metabolism and nutrition disorders</i>	
common	<i>hypertriglyceridaemia*</i>
uncommon	<i>hypercholesterolaemia*</i>
<i>Psychiatric disorders</i>	
Common	Abnormal dreams, anxiety, depression, insomnia*
Uncommon	Affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, <i>psychosis</i> [†] , suicide attempt, suicide ideation*
Rare	<i>Delusion</i> [‡] , <i>neurosis</i> [‡] , <i>completed suicide</i> ^{‡,*}
<i>Nervous system disorders</i>	
Common	<i>Cerebellar co-ordination and balance disturbances</i> [†] , disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%)*
Uncommon	Agitation, amnesia, ataxia, co-ordination abnormal, convulsions, thinking abnormal*, <i>tremor</i> [†]
<i>Eye disorders</i>	
Uncommon	Vision blurred
<i>Ear and labyrinth disorders</i>	
Uncommon	<i>Tinnitus</i> [†] , vertigo
<i>Vascular disorders</i>	
Uncommon	<i>Flushing</i> [†]
<i>Gastrointestinal disorders</i>	
Common	Abdominal pain, diarrhoea, nausea, vomiting
Uncommon	Pancreatitis

<i>Hepatobiliary disorders</i>	
common	aspartate aminotransferase (AST) increased*, alanine aminotransferase (ALT) increased*, gamma-glutamyltransferase (GGT) increased*
Uncommon	Hepatitis acute
Rare	<i>Hepatic failure</i> ^{†,*}
<i>Skin and subcutaneous tissue disorders</i>	
Very common	Rash (11.6%)*
Common	Pruritus
Uncommon	Erythema multiforme, Stevens-Johnson syndrome*
Rare	<i>Photoallergic dermatitis</i> [†]
<i>Reproductive system and breast disorders</i>	
Uncommon	Gynaecomastia
<i>General disorders and administration site conditions</i>	
Common	Fatigue

*,[†], [‡] See section c. Description of selected adverse reactions for more details.

c. Description of selected adverse reactions

Information regarding post-marketing surveillance

[†]These adverse reactions were identified through post-marketing surveillance; however, the frequencies were determined using data from 16 clinical trials (n=3,969).

[‡]These adverse reactions were identified through post-marketing surveillance but not reported as drug-related events for efavirenz-treated patients in 16 clinical trials. The frequency category of "rare" was defined per A Guideline on Summary of Product Characteristics (SmPC) (rev. 2, Sept. 2009) on the basis of an estimated upper bound of the 95% confidence interval for 0 events given the number of patients treated with efavirenz in these clinical trials (n=3,969).

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 re-initiated 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. Reported rates of recurrent rash following a switch from nevirapine to efavirenz therapy, primarily based on retrospective cohort data from published literature, range from 13 to 18%, comparable to the rate observed in patients treated with efavirenz in clinical studies (see section 4.4).

Psychiatric symptoms

Serious psychiatric adverse reactions have been reported in patients treated with efavirenz. In controlled trials, the frequency of specific serious psychiatric events were:

	Efavirenz regimen (n=1,008)	Control regimen (n=635)
- 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 reactions with frequencies 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 adverse reactions 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% (severe 2%) of patients compared to 9% (severe 1%) of patients receiving control regimens. In clinical studies 2% of patients treated with efavirenz discontinued therapy due to such 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 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 (see section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit.

Analysis of long-term data 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.

Hepatic failure

A few of the post-marketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

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. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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 (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Laboratory test abnormalities

Liver enzymes: Elevations of AST and 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 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.

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-naïve 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.

d. Paediatric population

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.

e. Other special populations

Liver enzymes in hepatitis B or C co-infected patients

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 co-infected patients in study 006, elevations in AST to greater than five times ULN developed in 13% of efavirenz-treated patients and in 7% of control, and elevations in ALT to greater than five times ULN developed in 20% and 7%, respectively. Among co-infected patients, 3% of those treated with efavirenz and 2% in the control arm discontinued because of liver disorders (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, Non-nucleoside reverse transcriptase inhibitors

ATC code: J05A G03

Mechanism of action

Efavirenz is a NNRTI of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases (α , β , γ or δ).

Antiviral activity

The free concentration of efavirenz required for 90 to 95% inhibition of wild type or zidovudine-resistant laboratory and clinical isolates *in vitro* ranged from 0.46 to 6.8 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures.

Resistance

The potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild-type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine-to-isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine-to-asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT.

K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. This mutation was observed in 90% of patients receiving efavirenz with virological failure. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medicines used in combination with efavirenz.

Cross-resistance

Cross-resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine-resistant clinical isolates examined were cross-resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross-resistant to efavirenz.

Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical studies who showed evidence of treatment failure (viral load rebound) were assessed for susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz-resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI-resistant isolates were found to have K103N or a valine-to-isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

The potential for cross-resistance between efavirenz and PIs is low because of the different enzyme targets involved. The potential for cross-resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action.

Clinical efficacy

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD₄ counts < 50 cells/mm³, or in PI or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited.

Two controlled studies (006 and ACTG 364) 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. Study 020 showed similar activity in NRTI-experienced patients over 24 weeks. 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, 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-naïve at study entry. The mean baseline CD₄ cell count was 341 cells/mm³ 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 2. 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 2: Efficacy results for study 006

Treatment regimen ^d	n	Responder rates (NC = F ^a)			Mean change from baseline-CD ₄ cell count Cells/mm ³ (S.E.M. ^c)	
		Plasma HIV-RNA				
		< 400 copies/ml (95% C.I. ^b)	< 50 copies/ml (95% C.I. ^b)			
		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 studies ACTG 364 and 020 are found in Table 3. Study ACTG 364 enrolled 196 patients who had been treated with NRTIs but not with PIs or NNRTIs. Study 020 enrolled 327 patients who had been treated with NRTIs but not with PIs or NNRTIs. Physicians were allowed to change their patient's NRTI regimen upon entry into the study. Responder rates were highest in patients who switched NRTIs.

Table 3: Efficacy results for studies ACTG 364 and 020

Study number/ Treatment regimens ^b	n	%	Responder rates (NC = F ^a)		Mean change from baseline-CD ₄ cell count	
			Plasma HIV-RNA (95% C.I. ^c)	% (95% C.I. ^c)	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)
Study 020 24 weeks			< 400 copies/ml	< 50 copies/ml		
EFV + IDV + NRTIs	157	60	(52, 68)	49 (41, 58)	104	(9.1)
IDV + NRTIs	170	51	(43, 59)	38 (30, 45)	77	(9.9)

^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.

Paediatric population

ACTG 382 is an ongoing uncontrolled study of 57 NRTI-experienced paediatric patients (3-16 years) which characterises the pharmacokinetics, antiviral activity and safety of efavirenz in combination with nelfinavir (20-30 mg/kg given three times a day) and one or more NRTIs. The starting dose of efavirenz was the equivalent of a 600 mg dose (adjusted from calculated body size based on weight). The response rate, based on the NC = F analysis of the percentage of patients with plasma HIV-RNA < 400 copies/ml at 48 weeks was 60% (95%, C.I. 47, 72), and 53% (C.I. 40, 66) based on percentage of patients with plasma HIV-RNA < 50 copies/ml. The mean CD₄ cell counts were increased by 63 ± 34.5 cells/mm³ from baseline. The durability of the response was similar to that seen in adult patients.

5.2 Pharmacokinetic properties

Absorption

Peak efavirenz plasma concentrations of 1.6-9.1 microM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1,600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3-5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6-7 days.

In HIV infected patients at steady-state, mean C_{max}, mean C_{min}, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily,

steady-state C_{\max} was 12.9 ± 3.7 microM (29%) [mean \pm S.D. (% C.V.)], steady-state C_{\min} was 5.6 ± 3.2 microM (57%), and AUC was 184 ± 73 microM·h (40%).

Effect of food

The AUC and C_{\max} of a single 600 mg dose of efavirenz film-coated tablets in uninfected volunteers was increased by 28% (90% CI: 22-33%) and 79% (90% CI: 58-102%), respectively, when given with a high-fat meal, relative to when given under fasted conditions (see section 4.4).

Distribution

Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients ($n = 9$) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Biotransformation

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. In *in vitro* studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce CYP3A4 and CYP2B6, resulting in the induction of its own metabolism which may be clinically relevant in some patients. In uninfected volunteers, multiple doses of 200-400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half-life compared with single dose administration (see below). Efavirenz has also been shown to induce UGT1A1. Exposures of raltegravir (a UGT1A1 substrate) are reduced in the presence of efavirenz (see section 4.5, table 1).

Although *in vitro* data suggest that efavirenz inhibits CYP2C9 and CYP2C19, there have been contradictory reports of both increased and decreased exposures to substrates of these enzymes when coadministered with efavirenz *in vivo*. The net effect of coadministration is not clear.

Elimination

Efavirenz has a relatively long terminal half-life of at least 52 hours after single doses and 40-55 hours after multiple doses. Approximately 14-34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

Hepatic impairment

In a single-dose study, half-life was doubled in the single patient with severe hepatic impairment (Child Pugh class C), indicating a potential for a much greater degree of accumulation. A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh class B or C) affects efavirenz pharmacokinetics.

Gender, race, elderly

Although limited data suggest that females as well as Asian and Pacific Island patients may have higher exposure to efavirenz, they do not appear to be less tolerant of efavirenz. Pharmacokinetic studies have not been performed in the elderly.

Paediatric population

In 49 paediatric patients receiving the equivalent of a 600 mg dose of efavirenz (dose adjusted from calculated body size based on weight), steady state C_{\max} was 14.1 microM, steady state C_{\min} was 5.6 microM, and AUC was 216 microM·h. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

5.3 Preclinical safety data

Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays.

Efavirenz induced foetal resorptions in rats. Malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, micro-ophthalmia was observed in another foetus, and cleft palate was observed in a third foetus. No malformations were observed in foetuses from efavirenz-treated rats and rabbits.

Biliary hyperplasia was observed in cynomolgus monkeys given efavirenz for ≥ 1 year at a dose resulting in mean AUC values approximately 2-fold greater than those in humans given the recommended dose. The biliary hyperplasia regressed upon cessation of dosing. Biliary fibrosis has been observed in rats. Non-sustained convulsions were observed in some monkeys receiving efavirenz for ≥ 1 year, at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose (see sections 4.4 and 4.8).

Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice. The mechanism of tumour formation and the potential relevance for humans are not known.

Carcinogenicity studies in male mice, male and female rats were negative. While the carcinogenic potential in humans is unknown, these data suggest that the clinical benefit of efavirenz outweighs the potential carcinogenic risk to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Cellulose, microcrystalline
Hydroxypropylcellulose
Sodium laurilsulfate
Sodium starch glycolate (Type A)
Poloxamer 407
Magnesium stearate

Film-coating

Opadry II 33G32531 yellow containing
Hypromellose

Lactose monohydrate
Titanium dioxide
Macrogol 3350
Glycerol triacetate
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque PVC/PVdC-aluminium or aluminium-aluminium blisters in a carton containing 30 or 90 film-coated tablets.

30 x 1 film-coated tablet in white opaque PVC/PVdC-aluminium or aluminium-aluminium perforated unit dose blisters.

90 x 1 film-coated tablet in white opaque PVC/PVdC-aluminium perforated unit dose blisters.

Multipack (bundle) containing 90 film-coated tablets (3 packs of 30 x 1 film-coated tablet) in white opaque PVC/PVdC-aluminium or aluminium-aluminium perforated unit dose blisters.

Multipack (carton) containing 90 film-coated tablets (3 packs of 30 x 1 film-coated tablet) in white opaque PVC/PVdC-aluminium or aluminium-aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Teva B.V., Swensweg 5, 2031GA Haarlem, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/742/001-011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 January 2012

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Teva Pharmaceutical Works Private Limited Company
Pallagi út 13
HU-4042 Debrecen
Hungary

TEVA UK Ltd
Brampton Road
Hampden Park, Eastbourne
East Sussex, BN22 9AG
United Kingdom

PLIVA Hrvatska d.o.o. (PLIVA Croatia Ltd.)
Prilaz baruna Filipovića 25
10000 Zagreb,
Croatia

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)**

Not applicable.

- Additional risk minimisation measures**

Not applicable

- Obligation to conduct post-authorisation measures**

Not applicable

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON FOR BLISTER PACK CONTAINING
OF <30><30x1><90><90 x 1> EFAVIRENZ TEVA 600 mg FILM-COATED TABLETS**

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz Teva 600 mg film-coated tablets
Efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg efavirenz.

3. LIST OF EXCIPIENTS

The tablet also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
30 x 1 film-coated-tablet s
90 x 1 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP {MM/YYYY}

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V., Swensweg 5, 2031GA Haarlem, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/742/001 (30 x 1 – blister PVC/PVDC/alu)
EU/1/11/742/002 (30 – blister PVC/PVDC/alu)
EU/1/11/742/003 (90 – blister PVC/PVDC/alu)
EU/1/11/742/006 (30 x 1 – blister alu/alu)
EU/1/11/742/007 (30 – blister alu/alu)
EU/1/11/742/008 (90 – blister alu/alu)
EU/1/11/742/011 (90 x 1 – blister PVC/PVDC/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Efavirenz Teva 600 mg film-coated tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER BUNDLE LABEL FOR MULTIPACKS OF 90 (3 PACKS OF 30 x 1 FILM-COATED TABLET) - WITH THE BLUE BOX****1. NAME OF THE MEDICINAL PRODUCT**

Efavirenz Teva 600 mg film-coated tablets
Efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg efavirenz.

3. LIST OF EXCIPIENTS

The tablet also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 90 (3 packs of 30 x 1) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP {MM/YYYY}

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V., Swensweg 5, 2031GA Haarlem, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/742/004 (bundle multi-pack – blister PVC/PVDC/alu)
EU/1/11/742/009 (bundle multi-pack – blister alu/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Efavirenz Teva 600 mg film-coated tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR MULTIPACKS OF 90 (3 PACKS OF 30 x 1 FILM-COATED TABLETS) - WITH THE BLUE BOX****1. NAME OF THE MEDICINAL PRODUCT**

Efavirenz Teva 600 mg film-coated tablets
Efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg efavirenz.

3. LIST OF EXCIPIENTS

The tablet also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 90 (3 packs of 30 x 1) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP {MM/YYYY}

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V., Swensweg 5, 2031GA Haarlem, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/742/005 (carton multi-pack – blister PVC/PVDC/alu)
EU/1/11/742/010 (carton multi-pack – blister alu/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Efavirenz Teva 600 mg film-coated tablets

PARTICULARS TO APPEAR ON THE OUTER CARTON**COMPONENT OF MULTIPACK OF 90 (3 PACKS OF 30 x 1 FILM-COATED TABLETS) - WITHOUT BLUE BOX****1. NAME OF THE MEDICINAL PRODUCT**

Efavirenz Teva 600 mg film-coated tablets
Efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg efavirenz.

3. LIST OF EXCIPIENTS

The tablet also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 film-coated tablets. Component of a multipack can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP {MM/YYYY}

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V., Swensweg 5, 2031GA Haarlem, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/742/001 (30 x 1 – blister PVC/PVDC/alu)
EU/1/11/742/006 (30 x 1 – blister alu/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Efavirenz Teva 600 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

EFAVIRENZ TEVA 600 mg FILM-COATED TABLET: BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz Teva 600 mg film-coated tablets
Efavirenz

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

Efavirenz Teva 600 mg film-coated tablets Efavirenz

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Efavirenz Teva is and what it is used for
2. What you need to know before you take Efavirenz Teva
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1. What Efavirenz Teva is and what it is used for

Efavirenz Teva, which contains the active substance efavirenz belongs to a class of antiretroviral medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). It is an **antiretroviral medicine that fights human immunodeficiency virus** (HIV-1) infection by reducing the amount of the virus in blood. It is used by adults, adolescents and children 3 years of age and older.

Your doctor has prescribed Efavirenz Teva for you because you have HIV infection. Efavirenz Teva taken in combination with other antiretroviral medicines reduces the amount of the virus in the blood. This will strengthen your immune system and reduce the risk of developing illnesses linked to HIV infection.

2. What you need to know before you take Efavirenz Teva

Do NOT take Efavirenz Teva

- **If you are allergic** (hypersensitive) to efavirenz or any of the other ingredients of this medicine (listed in section 6). Contact your doctor or pharmacist for advice.
 - **If you have severe liver disease.**
 - **If you are currently taking** any of the following medicines:
 - **Astemizole or terfenadine** (used to treat allergy symptoms)
 - **Bepridil** (used to treat heart disease)
 - **Cisapride** (used to treat heartburn)
 - **Ergot alkaloids** (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraine and cluster headaches)
 - **Midazolam or triazolam** (used to help you sleep)
 - **Pimozide** (used to treat certain mental conditions)
 - **St John's wort (*Hypericum perforatum*)** (a herbal remedy for depression and anxiety)
- If you are taking any of these medicines, tell your doctor immediately.** Taking these medicines with Efavirenz Teva could create the potential for serious and/or life-threatening side effects or stop Efavirenz Teva from working properly.

Warnings and precautions

Talk to your doctor before taking Efavirenz Teva

- **Efavirenz Teva must be taken with other medicines that act against the HIV virus.** If Efavirenz Teva is started because your current treatment has not prevented the virus from multiplying, another medicine you have not taken before must be started at the same time.
- **You can still pass on HIV** when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people. This medicine is not a cure for HIV infection and you may continue to develop infections or other illnesses associated with HIV disease.
- You must remain under the care of your doctor while taking Efavirenz Teva.
- **Tell your doctor:**
 - **if you have a history of mental illness**, including depression, or of substance or alcohol abuse. Tell your doctor immediately if you feel depressed, have suicidal thoughts or have strange thoughts (see section 4, Possible side effects).
 - **if you have a history of convulsions (fits or seizures)** or if you are being treated with anticonvulsant therapy such as carbamazepine, phenobarbital and phenytoin. If you are taking any of these medicines, your doctor may need to check the level of anticonvulsant medicine in your blood to ensure that it is not affected while taking Efavirenz Teva. Your doctor may give you a different anticonvulsant.
 - **if you have a history of liver disease, including active chronic hepatitis.** Patients with chronic hepatitis B or C and treated with combination antiretroviral agents have a higher risk for severe and potentially life-threatening liver problems. Your doctor may conduct blood tests in order to check how well your liver is working or may switch you to another medicine. **If you have severe liver disease, do not take Efavirenz Teva** (see section 2, Do not take Efavirenz Teva).
- **Once you start taking Efavirenz Teva, look out for:**
 - **signs of dizziness, difficulty sleeping, drowsiness, difficulty concentrating or abnormal dreaming.** These side effects may start in the first 1 or 2 days of treatment and usually go away after the first 2 to 4 weeks.
 - **any signs of skin rash.** If you see any signs of a severe rash with blistering or fever, stop taking Efavirenz Teva and tell your doctor at once. If you had a rash while taking another NNRTI, you may be at a higher risk of getting a rash with Efavirenz Teva.
 - **any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please tell your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.
 - **changes in body fat.** Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Tell your doctor if you notice changes in your body fat.
 - **bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint

stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Children and adolescents

Efavirenz Teva film-coated tablets are not recommended for children under the age of 3 years or weighing less than 13 kg because it has not been adequately studied in these patients.

Other medicines and Efavirenz Teva

You must not take Efavirenz Teva with certain medicines. These are listed under "Do not take Efavirenz Teva", at the start of Section 2. They include some common medicines and a herbal remedy (St. John's wort) which can cause serious interactions.

Tell your doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines.

Efavirenz Teva may interact with other medicines, including herbal preparations such as *Ginkgo biloba* extracts. As a result, the amounts of Efavirenz Teva or other medicines in your blood may be affected. This may stop the medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels. **It is important to tell your doctor or pharmacist if you are taking any of the following:**

- **Other medicines used for HIV infection:**
 - protease inhibitors: darunavir, indinavir, lopinavir/ritonavir, ritonavir, ritonavir-boosted atazanavir, saquinavir or fosamprenavir/saquinavir. Your doctor may consider giving you an alternative medicine or changing the dose of the protease inhibitors.
 - maraviroc
 - the combination tablet containing efavirenz, emtricitabine, and tenofovir should not be taken with Efavirenz Teva unless recommended by your doctor since it contains efavirenz, the active ingredient of Efavirenz Teva.
- **Medicines used to treat infection with the hepatitis C virus:** boceprevir, telaprevir, simeprevir
- **Medicines used to treat bacterial infections** including tuberculosis and AIDS-related mycobacterium avium complex: clarithromycin, rifabutin, rifampicin. Your doctor may consider changing your dose or giving you an alternative antibiotic. In addition, your doctor may prescribe a higher dose of Efavirenz Teva.
- **Medicines used to treat fungal infections (antifungals):**
 - voriconazole. Efavirenz Teva may reduce the amount of voriconazole in your blood and voriconazole may increase the amount of efavirenz in your blood. If you take these two medicines together, the dose of voriconazole must be increased and the dose of efavirenz must be reduced. You must check with your doctor first.
 - itraconazole. Efavirenz Teva may reduce the amount of itraconazole in your blood.
 - posaconazole. Efavirenz Teva may reduce the amount of posaconazole in your blood.
- **Medicines used to treat malaria:**
 - artemether/lumefantrine: Efavirenz Teva may reduce the amount of artemether/lumefantrine in your blood
 - atovaquone/proguanil: Efavirenz Teva may reduce the amount of atovaquone/proguanil in your blood.
- **Medicines used to treat convulsions/seizures (anticonvulsants):** carbamazepine, phenytoin, phenobarbital. Efavirenz Teva can reduce or increase the amount of anticonvulsant in your blood. Carbamazepine may make Efavirenz Teva less likely to work. Your doctor may need to consider giving you a different anticonvulsant.
- **Medicines used to lower blood fats (also called statins):** atorvastatin, pravastatin, simvastatin. Efavirenz Teva can reduce the amount of statins in your blood. Your doctor will check your cholesterol levels and will consider changing the dose of your statin, if needed.
- **Methadone** (a medicine used to treat opiate addiction): your doctor may need to change your dose of methadone.

- **Sertraline** (a medicine used to treat depression): your doctor may need to change your dose of sertraline.
- **Bupropion** (a medicine used to treat depression or to help you stop smoking): your doctor may need to change your dose of bupropion.
- **Diltiazem or similar medicines (called calcium channel blockers which are medicines typically used for high blood pressure or heart problems)**: when you start taking Efavirenz Teva, your doctor may need to adjust your dose of the calcium channel blocker.
- **Immunosuppressants such as ciclosporin, sirolimus, or tacrolimus** (medicines used to prevent organ transplant rejection): when you start or stop taking Efavirenz Teva, your doctor will closely monitor your plasma levels of the immunosuppressant and may need to adjust its dose.
- **Hormonal contraceptive, such as birth control pills, an injected contraceptive (for example, Depo-Provera), or a contraceptive implant (for example, Implanon)**: you must also use a reliable barrier method of contraception (see Pregnancy, breast-feeding and fertility). Efavirenz Teva may make hormonal contraceptives less likely to work. Pregnancies have occurred in women taking Efavirenz Teva while using a contraceptive implant, although it has not been established that the Efavirenz Teva therapy caused the contraceptive to fail.
- **Warfarin or acenocoumarol** (medicines used to reduce clotting of the blood): your doctor may need to adjust your dose of warfarin or acenocoumarol.
- **Ginkgo biloba extracts** (a herbal preparation)

Efavirenz Teva with food and drink

Taking Efavirenz Teva on an empty stomach may reduce the undesirable effects. Grapefruit juice should be avoided when taking Efavirenz Teva.

Pregnancy, breast-feeding and fertility

Women should not get pregnant during treatment with Efavirenz Teva and for **12 weeks thereafter**. Your doctor may require you to take a pregnancy test to ensure you are not pregnant before starting treatment with Efavirenz Teva.

If you could get pregnant while receiving Efavirenz Teva, you need to use a reliable form of barrier contraception (for example, a condom) with other methods of contraception including oral (pill) or other hormonal contraceptives (for example, implants, injection). Efavirenz may remain in your blood for a time after therapy is stopped. Therefore, you should continue to use contraceptive measures, as above, for 12 weeks after you stop taking Efavirenz Teva.

Tell your doctor immediately if you are pregnant or intend to become pregnant. If you are pregnant, you should take Efavirenz Teva only if you and your doctor decide it is clearly needed. Ask your doctor or pharmacist for advice before taking any medicine.

Serious birth defects have been seen in unborn animals and in the babies of women treated with efavirenz or a combination medicine containing efavirenz, emtricitabine and tenofovir during pregnancy. If you have taken Efavirenz Teva or the combination tablet containing efavirenz, emtricitabine, and tenofovir during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child.

You should not breast-feed your baby if you are taking Efavirenz Teva.

Driving and using machines

Efavirenz Teva contains efavirenz and may cause dizziness, impaired concentration, and drowsiness. If you are affected, do not drive and do not use any tools or machines.

Efavirenz Teva contains

10.5 mg lactose monohydrate (equivalent to 9.98 mg lactose anhydrous) in each 600 mg daily dose.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. Individuals with these conditions may take efavirenz oral solution, which is free from lactose.

3. How to take Efavirenz Teva

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor will give you instructions for proper dosing.

-The dose for adults is 600 mg once daily.

- The dose for Efavirenz Teva may need to be increased or decreased if you are also taking certain medicines (see Other medicines and Efavirenz Teva).

- Efavirenz Teva is for oral use. It is recommended to be taken on an empty stomach preferably at bedtime. This may make some side effects (for example, dizziness, drowsiness) less troublesome. An empty stomach is commonly defined as 1 hour before or 2 hours after a meal.
- It is recommended that the tablet be swallowed whole with water.
- Efavirenz Teva must be taken every day.
- Efavirenz Teva should never be used alone to treat HIV. It must always be taken in combination with other anti-HIV medicines.

Use in children and adolescents

- Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg.
- The dose for children weighing 40 kg or more is 600 mg once daily.

If you take more Efavirenz Teva than you should

If you take too much Efavirenz Teva, contact your doctor or nearest emergency department for advice. Keep the medicine container with you so that you can easily describe what you have taken.

If you forget to take Efavirenz Teva

Try not to miss a dose. **If you do miss a dose**, take the next dose as soon as possible, but do not take a double dose to make up for a forgotten dose. If you need help in planning the best times to take your medicine, ask your doctor or pharmacist.

If you stop taking Efavirenz Teva

When your Efavirenz Teva supply starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When treating HIV infection, it is not always possible to tell whether some of the unwanted effects are caused by Efavirenz Teva or by other medicines that you are taking at the same time, or by the HIV disease itself.

The most notable unwanted effects reported with efavirenz in combination with other anti-HIV medicines are skin rash and nervous system symptoms.

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

The nervous system symptoms tend to occur when treatment is first started, but generally decrease in the first few weeks. In one study, nervous system symptoms often occurred during the first 1-3 hours after taking a dose. If you are affected your doctor may suggest that you take Efavirenz Teva at bedtime and on an empty stomach. Some patients have more serious symptoms that may affect mood or the ability to think clearly. Some patients have actually committed suicide. These problems tend to occur more often in those who have a history of mental illness. Always notify your doctor immediately if you have these symptoms or any side effects while taking Efavirenz Teva.

Tell your doctor if you notice any of the following side effects:

Very common (affects more than 1 user in 10)

- skin rash

Common (affects 1 to 10 users in 100)

- abnormal dreams, difficulty concentrating, dizziness, headache, difficulty sleeping, drowsiness, problems with co-ordination or balance
- stomach pain, diarrhoea, feeling sick (nausea), vomiting
- itching
- tiredness
- feeling anxious, feeling depressed

Tests may show:

- increased liver enzymes in the blood
- increased triglycerides (fatty acids) in the blood

Uncommon (affects 1 to 10 users in 1,000)

- nervousness, forgetfulness, confusion, fitting (seizures), abnormal thoughts
- blurred vision
- a feeling of spinning or tilting (vertigo)
- pain in the abdomen (stomach) caused by inflammation of the pancreas
- allergic reaction (hypersensitivity) that may cause severe skin reactions (erythema multiforme, Stevens-Johnson syndrome)
- yellow skin or eyes, itching, or pain in the abdomen (stomach) caused by inflammation of the liver
- breast enlargement in males
- angry behaviour, mood being affected, seeing or hearing things that are not really there (hallucinations), mania (mental condition characterised by episodes of overactivity, elation or irritability), paranoia, suicidal thoughts
- whistling, ringing or other persistent noise in the ears
- tremor (shaking)
- flushing

Tests may show:

- increased cholesterol in the blood

Rare (affects 1 to 10 users in 10,000)

- itchy rash caused by a reaction to sunlight
- liver failure, in some cases leading to death or liver transplant, has occurred with efavirenz. Most cases occurred in patients who already had liver disease, but there have been a few reports in patients without any existing liver disease.
- unexplained feelings of distress not associated with hallucinations, but it may be difficult to think clearly or sensibly
- suicide

Combination antiretroviral therapy may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face, gain fat around the abdomen (tummy) and other internal organs, get larger breasts or fatty lumps on the back of the neck ('buffalo hump'). The cause and long-term health effects of these conditions are not yet known.

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, increased fat levels in the blood (hyperlipaemia) and resistance to insulin. Your doctor will test for these changes.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Efavirenz Teva

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and on the carton after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Efavirenz Teva contains

- Each Efavirenz Teva film-coated tablet contains 600 mg of the active substance efavirenz.
- The other ingredients are cellulose microcrystalline, hydroxypropylcellulose, sodium laurilsulfate, sodium starch glycolate (Type A), poloxamer 407 and magnesium stearate in the core. The film-coating agent is Opadry II 33G32531 yellow which contains hypromellose, lactose monohydrate, titanium dioxide, macrogol 3350, glycerol triacetate and iron oxide yellow.

What Efavirenz Teva looks like and contents of the pack

- Film-coated tablet: yellow, capsule-shaped, film-coated tablet debossed with "Teva" on one side and "7541" on the other
- Efavirenz Teva is available in pack sizes of 30, 90 film-coated tablets or 30 x 1 / 90 x 1 film-coated tablets (in perforated unit dose blisters) or a multi-pack bundle or carton containing 90 film-coated tablets (3 packs of 30 x 1 film-coated tablet). Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

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Manufacturer:

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PLIVA Hrvatska d.o.o. (PLIVA Croatia Ltd.), Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>