ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 50 mg hard capsules
SUSTIVA 100 mg hard capsules
SUSTIVA 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SUSTIVA 50 mg hard capsules
Each hard capsule contains 50 mg of efavirenz.

Excipient with known effect
Each hard capsule contains 28.5 mg of lactose (as monohydrate).

SUSTIVA 100 mg hard capsules
Each hard capsule contains 100 mg of efavirenz.

Excipient with known effect
Each hard capsule contains 57.0 mg of lactose (as monohydrate).

SUSTIVA 200 mg hard capsules
Each hard capsule contains 200 mg of efavirenz.

Excipient with known effect
Each hard capsule contains 114.0 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

SUSTIVA 50 mg hard capsules
Dark yellow and white, printed with "SUSTIVA" on the dark yellow cap and "50 mg" on the white body.

SUSTIVA 100 mg hard capsules
White, printed with "SUSTIVA" on the body and "100 mg" on the cap.

SUSTIVA 200 mg hard capsules
Dark yellow, printed with "SUSTIVA" on the body and "200 mg" on the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUSTIVA is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 months of age and older and weighing at least 3.5 kg.

SUSTIVA has not been adequately studied in patients with advanced HIV disease, namely in patients with CD4 counts < 50 cells/mm^3, 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 SUSTIVA.

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

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.

Dose adjustment

If efavirenz is coadministered 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 coadministered 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).

Children and adolescents (3 months to 17 years)

The recommended dose of efavirenz in combination with a PI and/or NRTIs for patients between 3 months and 17 years of age is described in Table 1. Efavirenz intact hard capsules must only be administered to children who are able to reliably swallow hard capsules.

Table 1: Paediatric dose to be administered once daily*

Body Weight **kg**	**efavirenz** **Dose (mg)**	**Number of Capsules or Tablets and Strength to Administer**
3.5 to < 5	100	one 100 mg capsule
5 to < 7.5	150	one 100 mg capsule + one 50 mg capsule
7.5 to < 15	200	one 200 mg capsule
15 to < 20	250	one 200 mg capsule + one 50 mg capsule
20 to < 25	300	three 100 mg capsules
25 to < 32.5	350	three 100 mg capsules + one 50 mg capsule
32.5 to < 40	400	two 200 mg capsules
≥ 40	600	one 600 mg tablet OR three 200 mg capsules

*For information on the bioavailability of the capsule contents mixed with food vehicles, see section 5.2.

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).

Paediatric population

The safety and efficacy of efavirenz in children below the age of 3 months or weighing less than 3.5 kg have not been established. No data are available.

Method of administration

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

Patients who cannot swallow

Capsule sprinkle: for patients at least 3 months old and weighing at least 3.5 kg who cannot swallow capsules, the capsule contents can be administered with a small amount of food using the capsule sprinkle method of administration (see section 6.6 for instructions). No additional food should be consumed for up to 2 hours after administration of efavirenz..

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-administraion 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).

Co-administration with elbasvir (EBR) and grazoprevir (GZR) due to the potential for significant decreases in plasma concentrations of EBR and GZR (see section 4.5).

Herbal preparations containing St. John's wort *(Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Patients with:
- a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- severe disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

Patients taking drugs that are known to prolong the QTc interval (proarrythmic).
These drugs include:

- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- certain non-sedating antihistamines (terfenadine, astemizole),
- cisapride,
- flecainide,
- certain antimalarials,
- methadone.

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. 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 is not recommended unless needed for dose adjustment (for example, with rifampicin).

Coadministration of sofosbuvir/velpatasvir with efavirenz is not recommended (see section 4.5).
Concomitant administration of velpatasvir/sofosbuvir/ voxilaprevir with efavirenz is not recommended (see section 4.5).
Coadministration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Coadministration of glecaprevir/pibrentasvir with efavirenz is not recommended (see section 4.5).

Concomitant use of *Ginkgo biloba* extracts 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.

<u>Rash</u>

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, psychosis-like behaviour and catatonia. 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 adult and paediatric 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 postmarketing 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.

QTc Prolongation

QTc prolongation has been observed with the use of efavirenz (see sections 4.5 and 5.1).

Consider alternatives to efavirenz for coadministration with a drug with a known risk of Torsade de Pointes or when to be administered to patients at higher risk of Torsade de Pointes.

Effect of food

The administration of efavirenz 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 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 and autoimmune hepatitis) 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.

Weight and metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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.

Elderly patients

Insufficient numbers of elderly 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 months of age or who weigh less than 3.5 kg. Therefore, efavirenz should not be given to children less than 3 months of age.

Rash was reported in 59 of 182 children (32%) treated with efavirenz and was severe in six 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.

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).

QT Prolonging Drugs

Efavirenz is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see section 4.3).

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).

Elbasvir/grazoprevir

Concomitant administration of efavirenz with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A4 induction. (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 2 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 2: 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 Cmin 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	Interaction not studied.	No dose adjustment is necessary for any of these medicinal products.
Fosamprenavir/Saquinavir/ Efavirenz	Interaction not studied.	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.
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.	No dose adjustment is necessary for efavirenz when given with indinavir or indinavir/ritonavir. See also ritonavir row below.

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**
Lopinavir/ritonavir soft capsules or oral solution/Efavirenz Lopinavir/ritonavir tablets/ Efavirenz (400/100 mg twice daily/600 mg once daily) (500/125 mg twice daily/600 mg once daily)	Substantial decrease in lopinavir exposure. Lopinavir concentrations: ↓ 30-40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz	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 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		

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**
Raltegravir/Efavirenz (400 mg single dose/ -)	Raltegravir: AUC: ↓ 36% C_{12}: ↓ 21% C_{max}: ↓ 36% (UGT1A1 induction)	No dose adjustment is necessary for raltegravir.
NRTIs and NNRTIs		
NRTIs/Efavirenz	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine, and tenofovir disoproxil. 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)	Boceprevir: AUC: ↔ 19%* C_{max}: ↔ 8% C_{min}: ↓ 44% Efavirenz: AUC: ↔ 20% C_{max}: ↔ 11% (CYP3A induction - effect on boceprevir) *0-8 hours No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of ≤25%	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)	Telaprevir (relative to 750 mg q8h): AUC: ↓ 18% (↓ 8 to ↓ 27) C_{max}: ↓ 14% (↓ 3 to ↓ 24) C_{min}: ↓ 25% (↓ 14 to ↓ 34)% Efavirenz: AUC: ↓ 18% (↓ 10 to ↓ 26) C_{max}: ↓ 24% (↓ 15 to ↓ 32) C_{min}: ↓ 10% (↑ 1 to ↓ 19)% (CYP3A induction by efavirenz)	If efavirenz and telaprevir are co-administered, telaprevir 1,125 mg every 8 hours should be used.

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**
Simeprevir/Efavirenz (150 mg once daily /600 mg once daily)	Simeprevir: AUC: ↓71% (↓67 to ↓74) Cmax: ↓51% (↓46 to ↓56) Cmin: ↓91% (↓88 to ↓92) Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of ≤25% (CYP3A4 enzyme induction)	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.
Sofosbuvir/ velpatasvir	↔sofosbuvir ↓velpatasvir ↔efavirenz	Concomitant administration of sofosbuvir/velpatasvir with efavirenz resulted in a reduction (approximately 50%) in the systemic exposure of velpatasvir. The mechanism of the effect on velpatasvir is induction of CYP3A and CYP2B6 by efavirenz. Coadministration of sofosbuvir/velpatasvir with efavirenz is not recommended. Refer to the prescribing information for sofosbuvir/velpatasvir for more information.
Velpatasvir/ sofosbuvir/ voxilaprevir	↓velpatasvir ↓voxilaprevir	Concomitant administration of velpatasvir/sofosbuvir/ voxilaprevir with efavirenz is not recommended, as it may decrease concentrations of velpatasvir and voxilaprevir. Refer to the prescribing information for velpatasvir/sofosbuvir/ voxilaprevir for more information.

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
Protease inhibitor : Elbasvir/ grazoprevir	↓elbasvir ↓grazoprevir ↔efavirenz	Concomitant administration of efavirenz with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A4 induction. Refer to the prescribing information for elbasvir/grazoprevir for more information.
Glecaprevir/pibrentasvir	↓glecaprevir ↓ pibrentasvir	Concomitant administration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Coadministration of glecaprevir/pibrentasvir with efavirenz is not recommended. Refer to the prescribing information for glecaprevir/pibrentasvir for more information.
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.

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
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, including 600 mg
Antifungals		
Itraconazole/Efavirenz (200 mg q12h/600 mg once daily)	Itraconazole: AUC: ↓ 39% (↓ 21 to ↓ 53) 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.	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

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**
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/Efavirenz (400 mg twice daily/300 mg once daily)	Voriconazole: AUC: ↓ 77% C_{max}: ↓ 61% Efavirenz: AUC: ↑ 44% C_{max}: ↑ 38% 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)	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.e., to 300 mg once daily. When treatment with voriconazole is stopped, the initial dose of efavirenz should be restored.
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% C_{max}: ↔ (CYP3A4 induction)	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.
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.

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
ACID REDUCING AGENTS		
Aluminium hydroxide-magnesium hydroxide-simethicone antacid/Efavirenz (30 ml single dose/400 mg single dose) Famotidine/Efavirenz (40 mg 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.
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 anticonvulsants that are substrates of CYP450 isoenzymes when co-administered with efavirenz.	When efavirenz is co-administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic 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.

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**
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 Reuptake 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.e. 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)	Diltiazem: AUC: ↓ 69% (↓ 55 to ↓ 79) C_{max}: ↓ 60% (↓ 50 to ↓ 68) C_{min}: ↓ 63% (↓ 44 to ↓ 75) Desacetyl diltiazem: AUC: ↓ 75% (↓ 59 to ↓ 84) C_{max}: ↓ 64% (↓ 57 to ↓ 69) C_{min}: ↓ 62% (↓ 44 to ↓ 75) N-monodesmethyl diltiazem: AUC: ↓ 37% (↓ 17 to ↓ 52) C_{max}: ↓ 28% (↓ 7 to ↓ 44) C_{min}: ↓ 37% (↓ 17 to ↓ 52) 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.	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 Co-A Reductase Inhibitors		
Atorvastatin/Efavirenz (10 mg once daily/600 mg once daily)	Atorvastatin: AUC: ↓ 43% (↓ 34 to ↓ 50) C_{max}: ↓ 12% (↓ 1 to ↓ 26) 2-hydroxy atorvastatin: AUC: ↓ 35% (↓ 13 to ↓ 40) C_{max}: ↓ 13% (↓ 0 to ↓ 23) 4-hydroxy atorvastatin: AUC: ↓ 4% (↓ 0 to ↓ 31) C_{max}: ↓ 47% (↓ 9 to ↓ 51) Total active HMG Co-A reductase inhibitors: AUC: ↓ 34% (↓ 21 to ↓ 41) C_{max}: ↓ 20% (↓ 2 to ↓ 26)	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)	Simvastatin: AUC: ↓ 69% (↓ 62 to ↓ 73) C_{max}: ↓ 76% (↓ 63 to ↓ 79) Simvastatin acid: AUC: ↓ 58% (↓ 39 to ↓ 68) C_{max}: ↓ 51% (↓ 32 to ↓ 58) Total active HMG Co-A reductase inhibitors: AUC: ↓ 60% (↓ 52 to ↓ 68) C_{max}: ↓ 62% (↓ 55 to ↓ 78) (CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values.	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: Ethinyloestradiol + Norgestimate/ Efavirenz (0.035 mg + 0.25 mg once daily/600 mg once daily)	Ethinyloestradiol: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 8% (↑ 14 to ↓ 25) Norelgestromin (active metabolite): AUC: ↓ 64% (↓ 62 to ↓ 67) C_{max}: ↓ 46% (↓ 39 to ↓ 52) C_{min}: ↓ 82% (↓ 79 to ↓ 85) Levonorgestrel (active metabolite): AUC: ↓ 83% (↓ 79 to ↓ 87) C_{max}: ↓ 80% (↓ 77 to ↓ 83) C_{min}: ↓ 86% (↓ 80 to ↓ 90) (induction of metabolism) Efavirenz: no clinically significant interaction. The clinical significance of these effects is not known.	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).
Implant: Etonogestrel/Efavirenz	Decreased exposure of etonogestrel may be expected (CYP3A4 induction). There have been occasional postmarketing 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).

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
IMMUNOSUPPRESSANTS		
Immunosuppressants metabolized by CYP3A4 (eg, cyclosporine, 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.	Concomitant administration with efavirenz should be avoided due to the risk for QTc prolongation (see section 4.3).
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

There have been seven retrospective reports of findings consistent with neural tube defects, including meningomyelocele, 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 can not be excluded. Breast-feeding should be discontinued during treatment with SUSTIVA. 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

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.

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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); or very rare (< 1/10,000).

Immune system disorders	
uncommon	hypersensitivity
Metabolism and nutrition disorders	
common	hypertriglyceridaemia*
uncommon	hypercholesterolaemia*
Psychiatric disorders	
common	abnormal dreams, anxiety, depression, insomnia*
uncommon	affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, *psychosis*[†], suicide attempt, suicide ideation, catatonia*
rare	*delusion*[‡], *neurosis*[‡], *completed suicide*[‡,]*
Nervous system disorders	
common	*cerebellar coordination and balance disturbances*[†], disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%)*
uncommon	agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal,* *tremor*[†]
Eye disorders	
uncommon	vision blurred
Ear and labyrinth disorders	
uncommon	*tinnitus*[†], vertigo
Vascular disorders	
uncommon	*flushing*[†]
Gastrointestinal disorders	
common	abdominal pain, diarrhoea, nausea, vomiting
uncommon	pancreatitis

Hepatobiliary disorders	
common	aspartate aminotransferase (AST) increased*, alanine aminotransferase (ALT) increased*, gamma-glutamyltransferase (GGT) increased*
uncommon	hepatitis acute
rare	*hepatic failure*[‡,]*
Skin and subcutaneous tissue disorders	
very common	rash (11.6%)*
common	pruritus
uncommon	erythema multiforme, Stevens-Johnson syndrome*
rare	*photoallergic dermatitis*[†]
Reproductive system and breast disorders	
uncommon	gynaecomastia
General disorders and administration site conditions	
common	Fatigue

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

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 reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when efavirenz is restarted.

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. 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, psychosis-like behaviour and catatonia.

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 postmarketing 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 and autoimmune hepatitis) 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).

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.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Paediatric population

Undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (59 of 182 (32%) treated with efavirenz) and was more often of higher grade than in adults (severe rash was reported in 6 of 182 (3.3%) of children). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered..

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 controls, 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 liverdisorders (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: J05AG03

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).

Cardiac Electrophysiology

The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see section 4.5).

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/mm^3, 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-naive at study entry. The mean baseline CD4 cell count was 341 cells/mm^3 and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 3. 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 3: Efficacy results for study 006

		Responder rates (NC = F[a]) Plasma HIV-RNA		Mean change from baseline-CD4 cell count cells/mm^3 (S.E.M.[c])
		< 400 copies/ml (95% C.I.[b])	< 50 copies/ml (95% C.I.[b])	
Treatment Regimen[d]	n	48 weeks	48 weeks	48 weeks
EFV + ZDV + 3TC	202	67% (60%, 73%)	62% (55%, 69%)	187 (11.8)
EFV + IDV	206	54% (47%, 61%)	48% (41%, 55%)	177 (11.3)
IDV + ZDV + 3TC	206	45% (38%, 52%)	40% (34%, 47%)	153 (12.3)

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

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

Efficacy results for studies ACTG 364 and 020 are found in Table 4. 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 4: Efficacy results for studies ACTG 364 and 020

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

Study AI266922 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in antiretroviral-naive and -experienced paediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with SUSTIVA. At baseline, median plasma HIV-1 RNA was 5.88 $\log_{10}$ copies/mL, median CD4+ cell count was 1144 cells/mm^3, and median CD4+ percentage was 25%. The median time on study therapy was 132 weeks; 27% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (21/37) and 46% (17/37), respectively. The median increase from baseline in CD4+ count at 48 weeks was 215 cells/mm^3 and the median increase in CD4+ percentage was 6%.

Study PACTG 1021 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in paediatric patients who were antiretroviral therapy naive. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with SUSTIVA. At baseline, median plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL, median CD4+ cell count was 367 cells/mm^3, and median CD4+ percentage was 18%. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 77% (33/43) and 70% (30/43), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 238 cells/mm^3 and the median increase in CD4+ percentage was 13%.

Study PACTG 382 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with nelfinavir and an NRTI in antiretroviral-naive and NRTI-experienced paediatric patients. One hundred two patients 3 months to 16 years of age (median 5.7 years) were treated with SUSTIVA. Eighty-seven percent of patients had received prior antiretroviral therapy. At baseline, median plasma HIV-1 RNA was 4.57 $\log_{10}$ copies/mL, median CD4+ cell count was 755 cells/mm^3, and median CD4+ percentage was 30%. The median time on study therapy was 118 weeks; 25% of patients discontinued before Week 48. Using an ITT analysis, the overall proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (58/102) and 43% (44/102), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 128 cells/mm^3 and the median increase in CD4+ percentage was 5%.

5.2 Pharmacokinetic properties

Absorption

Peak efavirenz plasma concentrations of 1.6 - 9.1 μM were attained by 5 hours following single oral doses of 100 mg to 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 μM (29%) [mean ± S.D. (% C.V.)], steady state C_{min} was 5.6 ± 3.2 μM (57%), and AUC was 184 ± 73 μM·h (40%).

Effect of food

The bioavailability of a single 600 mg dose of efavirenz hard capsules in uninfected volunteers was increased 22% and 17%, respectively, when given with a meal of high fat or normal composition, relative to the bioavailability of a 600 mg dose given under fasted conditions (see section 4.4).

Bioavailability of hard capsule contents mixed with food vehicles

In healthy adult subjects, the efavirenz AUC when administered as the contents of three 200 mg hard capsules mixed with 2 teaspoons of certain food vehicles (applesauce, grape jelly, yogurt or infant formula) met bioequivalency criteria for the AUC of the intact capsule formulation administered under fasted conditions.

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 2).
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

The pharmacokinetic parameters for efavirenz at steady state in paediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 5 by weight ranges that correspond to the recommended doses.

Table 5: Predicted steady-state pharmacokinetics of efavirenz (capsules/capsule sprinkles) in HIV-infected paediatric patients

Body Weight	Dose	Mean $AUC_{(0-24)}$ µM·h	Mean C_{max} µg/mL	Mean C_{min} µg/mL
3.5-5 kg	100 mg	220.52	5.81	2.43
5-7.5 kg	150 mg	262.62	7.07	2.71
7.5-10 kg	200 mg	284.28	7.75	2.87
10-15 kg	200 mg	238.14	6.54	2.32
15-20 kg	250 mg	233.98	6.47	2.3
20-25 kg	300 mg	257.56	7.04	2.55
25-32.5 kg	350 mg	262.37	7.12	2.68
32.5-40 kg	400 mg	259.79	6.96	2.69
>40 kg	600 mg	254.78	6.57	2.82

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, microophthalmia 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

SUSTIVA 50 mg hard capsules

Capsule core: Sodium laurilsulfate, Lactose monohydrate, Magnesium stearate, Sodium starch glycolate

Capsule shell: Gelatine, Sodium laurilsulfate, Yellow iron oxide (E172), Titanium dioxide (E171), Silicon dioxide (E551)

Printing ink: Cochineal carminic acid (E120), Indigo carmine (E132), Titanium dioxide (E171)

SUSTIVA 100 mg hard capsules
Capsule core: Sodium laurilsulfate, Lactose monohydrate, Magnesium stearate, Sodium starch glycolate

Capsule shell: Gelatine, Sodium laurilsulfate, Titanium dioxide (E171), Silicon dioxide (E551)

Printing ink: Cochineal carminic acid (E120), Indigo carmine (E132), Titanium dioxide (E171)

SUSTIVA 200 mg hard capsules
Capsule core: Sodium laurilsulfate, Lactose monohydrate, Magnesium stearate, Sodium starch glycolate

Capsule shell: Gelatine, Sodium laurilsulfate, Yellow iron oxide (E172), Silicon dioxide (E551)

Printing ink: Cochineal carminic acid (E120), Indigo carmine (E132), Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

SUSTIVA 50 mg hard capsules
SUSTIVA 100 mg hard capsules
3 years.

SUSTIVA 200 mg hard capsules
For bottles: 3 years.
For blisters: 2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and content of container

SUSTIVA 50 mg hard capsules
HDPE bottles with a child-resistant polypropylene closure. Each carton contains 1 bottle of 30 hard capsules.

SUSTIVA 100 mg hard capsules
HDPE bottles with a child-resistant polypropylene closure. Each carton contains 1 bottle of 30 hard capsules.

SUSTIVA 200 mg hard capsules
HDPE bottles with a child-resistant polypropylene closure. Each carton contains 1 bottle of 90 hard capsules.
Packs of 42 x 1 hard capsules in aluminium/PVC 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.

Use in the paediatric population

For patients at least 3 months old and weighing at least 3.5 kg who cannot swallow capsules, the capsule contents can be administered with a small amount (1-2 teaspoons) of food using the capsule sprinkle method of administration. Patients and caregivers must be instructed to open the capsule carefully to avoid spillage or dispersion of the capsule contents into the air. It is recommended to hold the capsule with the cap facing up and to pull the cap away from the body of the capsule, and to mix the capsule contents with food in a small container. The mixture should be administered as soon as possible, but no more than 30 minutes after mixing. After administration of the efavirenz-food mixture, an additional small amount (approximately 2 teaspoons) of food must be added to the empty mixing container, stirred to disperse any remaining residue of the medicinal product, and administered to the patient. No additional food should be consumed for up to 2 hours after administration of efavirenz.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15
D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 May 1999
Date of latest renewal: 23 April 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 600 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of efavirenz.

Excipient with known effect
Each film-coated tablet contains 249.6 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Dark yellow, capsule-shaped, printed with “SUSTIVA” on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUSTIVA is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 months of age and older and weighing at least 3.5 kg.

SUSTIVA has not been adequately studied in patients with advanced HIV disease, namely in patients with CD4 counts < 50 cells/mm^3, 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 SUSTIVA.

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 coadministered 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 coadministered 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).

Paediatric population

The safety and efficacy of efavirenz in children below the age of 3 months or weighing less than 3.5 kg have not been established. No data are available.

Method of administration

It is recommended that efavirenz be taken on an empty stomach. The increased efavirenz concentrations observed following administration of efavirenz with food may lead to an increase in frequency of adverse 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-administraion 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).

Co-administration with elbasvir (EBR) and grazoprevir (GZR) due to the potential for significant decreases in plasma concentrations of EBR and GZR (see section 4.5).

Herbal preparations containing St. John's wort *(Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Patients with:
- a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.

- a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- severe disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

Patients taking drugs that are known to prolong the QTc interval (proarrythmic).
These drugs include:

- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- certain non-sedating antihistamines (terfenadine, astemizole),
- cisapride,
- flecainide,
- certain antimalarials,
- methadone.

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. 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 is not recommended unless needed for dose adjustment (for example, with rifampicin).

Coadministration of sofosbuvir/velpatasvir with efavirenz is not recommended (see section 4.5). Concomitant administration of velpatasvir/sofosbuvir/ voxilaprevir with efavirenz is not recommended (see section 4.5).

Coadministration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Coadministration of glecaprevir/pibrentasvir with efavirenz is not recommended (see section 4.5).

Concomitant use of *Ginkgo biloba* extracts 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.

<u>Rash</u>

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, psychosis-like behaviour and catatonia. 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 adult and paediatric 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 postmarketing 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.

QTc Prolongation

QTc prolongation has been observed with the use of efavirenz (see sections 4.5 and 5.1).

Consider alternatives to efavirenz for coadministration with a drug with a known risk of Torsade de Pointes or when to be administered to patients at higher risk of Torsade de Pointes.

Effect of food

The administration of efavirenz 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 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 and autoimmune hepatitis) 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.

Weight and metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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.

Elderly patients

Insufficient numbers of elderly 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 months of age or who weigh less than 3.5 kg. Therefore, efavirenz should not be given to children less than 3 months of age. Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg.

Rash was reported in 59 of 182 children (32%) treated with efavirenz and was severe in six 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.

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).

QT Prolonging Drugs

Efavirenz is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see section 4.3).

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).

Elbasvir/grazoprevir

Concomitant administration of efavirenz with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A4 induction. (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 Cmin 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	Interaction not studied.	No dose adjustment is necessary for any of these medicinal products.
Fosamprenavir/Saquinavir/ Efavirenz	Interaction not studied.	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.
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.	No dose adjustment is necessary for efavirenz when given with indinavir or indinavir/ritonavir. See also ritonavir row below.

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**
Lopinavir/ritonavir soft capsules or oral solution/Efavirenz Lopinavir/ritonavir tablets/ Efavirenz (400/100 mg twice daily/600 mg once daily) (500/125 mg twice daily/600 mg once daily)	Substantial decrease in lopinavir exposure. Lopinavir concentrations: ↓ 30-40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz	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 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		

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
Raltegravir/Efavirenz (400 mg single dose/ -)	Raltegravir: AUC: ↓ 36% C_{12}: ↓ 21% C_{max}: ↓ 36% (UGT1A1 induction)	No dose adjustment is necessary for raltegravir.
NRTIs and NNRTIs		
NRTIs/Efavirenz	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine, and tenofovir disoproxil. 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)	Boceprevir: AUC: ↔ 19%* C_{max}: ↔ 8% C_{min}: ↓ 44% Efavirenz: AUC: ↔ 20% C_{max}: ↔ 11% (CYP3A induction - effect on boceprevir) *0-8 hours No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of ≤25%	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)	Telaprevir (relative to 750 mg q8h): AUC: ↓ 18% (↓ 8 to ↓ 27) C_{max}: ↓ 14% (↓ 3 to ↓ 24) C_{min}: ↓ 25% (↓ 14 to ↓ 34)% Efavirenz: AUC: ↓ 18% (↓ 10 to ↓ 26) C_{max}: ↓ 24% (↓ 15 to ↓ 32) C_{min}: ↓ 10% (↑ 1 to ↓ 19)% (CYP3A induction by efavirenz)	If efavirenz and telaprevir are co-administered, telaprevir 1,125 mg every 8 hours should be used.

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**
Simeprevir/Efavirenz (150 mg once daily /600 mg once daily)	Simeprevir: AUC: ↓71% (↓67 to ↓74) Cmax: ↓51% (↓46 to ↓56) Cmin: ↓91% (↓88 to ↓92) Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of ≤25% (CYP3A4 enzyme induction)	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.
Sofosbuvir/ velpatasvir	↔sofosbuvir ↓velpatasvir ↔efavirenz	Concomitant administration of sofosbuvir/velpatasvir with efavirenz resulted in a reduction (approximately 50%) in the systemic exposure of velpatasvir. The mechanism of the effect on velpatasvir is induction of CYP3A and CYP2B6 by efavirenz. Coadministration of sofosbuvir/velpatasvir with efavirenz is not recommended. Refer to the prescribing information for sofosbuvir/velpatasvir for more information.
Velpatasvir/ sofosbuvir/ voxilaprevir	↓velpatasvir ↓voxilaprevir	Concomitant administration of velpatasvir/sofosbuvir/ voxilaprevir with efavirenz is not recommended, as it may decrease concentrations of velpatasvir and voxilaprevir. Refer to the prescribing information for velpatasvir/sofosbuvir/ voxilaprevir for more information.

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
Protease inhibitor : Elbasvir/ grazoprevir	↓elbasvir ↓grazoprevir ↔efavirenz	Concomitant administration of efavirenz with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A4 induction. Refer to the prescribing information for elbasvir/grazoprevir for more information.
Glecaprevir/pibrentasvir	↓glecaprevir ↓ pibrentasvir	Concomitant administration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Coadministration of glecaprevir/pibrentasvir with efavirenz is not recommended. Refer to the prescribing information for glecaprevir/pibrentasvir for more information.
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.

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
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, including 600 mg.
Antifungals		
Itraconazole/Efavirenz (200 mg q12h/600 mg once daily)	Itraconazole: AUC: ↓ 39% (↓ 21 to ↓ 53) 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.	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

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**
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/Efavirenz (400 mg twice daily/300 mg once daily)	Voriconazole: AUC: ↓ 77% C_{max}: ↓ 61% Efavirenz: AUC: ↑ 44% C_{max}: ↑ 38% 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)	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.e., to 300 mg once daily. When treatment with voriconazole is stopped, the initial dose of efavirenz should be restored.
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% C_{max}: ↔ (CYP3A4 induction)	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.
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.

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
ACID REDUCING AGENTS		
Aluminium hydroxide-magnesium hydroxide-simethicone antacid/Efavirenz (30 ml single dose/400 mg single dose) Famotidine/Efavirenz (40 mg 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.
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 anticonvulsants that are substrates of CYP450 isoenzymes when co-administered with efavirenz.	When efavirenz is co-administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic 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.

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
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 Reuptake 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.e. 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)	Diltiazem: AUC: ↓ 69% (↓ 55 to ↓ 79) C_{max}: ↓ 60% (↓ 50 to ↓ 68) C_{min}: ↓ 63% (↓ 44 to ↓ 75) Desacetyl diltiazem: AUC: ↓ 75% (↓ 59 to ↓ 84) C_{max}: ↓ 64% (↓ 57 to ↓ 69) C_{min}: ↓ 62% (↓ 44 to ↓ 75) N-monodesmethyl diltiazem: AUC: ↓ 37% (↓ 17 to ↓ 52) C_{max}: ↓ 28% (↓ 7 to ↓ 44) C_{min}: ↓ 37% (↓ 17 to ↓ 52) 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.	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 Co-A Reductase Inhibitors		
Atorvastatin/Efavirenz (10 mg once daily/600 mg once daily)	Atorvastatin: AUC: ↓ 43% (↓ 34 to ↓ 50) C_{max}: ↓ 12% (↓ 1 to ↓ 26) 2-hydroxy atorvastatin: AUC: ↓ 35% (↓ 13 to ↓ 40) C_{max}: ↓ 13% (↓ 0 to ↓ 23) 4-hydroxy atorvastatin: AUC: ↓ 4% (↓ 0 to ↓ 31) C_{max}: ↓ 47% (↓ 9 to ↓ 51) Total active HMG Co-A reductase inhibitors: AUC: ↓ 34% (↓ 21 to ↓ 41) C_{max}: ↓ 20% (↓ 2 to ↓ 26)	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)	Simvastatin: AUC: ↓ 69% (↓ 62 to ↓ 73) C_{max}: ↓ 76% (↓ 63 to ↓ 79) Simvastatin acid: AUC: ↓ 58% (↓ 39 to ↓ 68) C_{max}: ↓ 51% (↓ 32 to ↓ 58) Total active HMG Co-A reductase inhibitors: AUC: ↓ 60% (↓ 52 to ↓ 68) C_{max}: ↓ 62% (↓ 55 to ↓ 78) (CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values.	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: Ethinyloestradiol + Norgestimate/ Efavirenz (0.035 mg + 0.25 mg once daily/600 mg once daily)	Ethinyloestradiol: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 8% (↑ 14 to ↓ 25) Norelgestromin (active metabolite): AUC: ↓ 64% (↓ 62 to ↓ 67) C_{max}: ↓ 46% (↓ 39 to ↓ 52) C_{min}: ↓ 82% (↓ 79 to ↓ 85) Levonorgestrel (active metabolite): AUC: ↓ 83% (↓ 79 to ↓ 87) C_{max}: ↓ 80% (↓ 77 to ↓ 83) C_{min}: ↓ 86% (↓ 80 to ↓ 90) (induction of metabolism) Efavirenz: no clinically significant interaction. The clinical significance of these effects is not known.	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).
Implant: Etonogestrel/Efavirenz	Decreased exposure of etonogestrel may be expected (CYP3A4 induction). There have been occasional postmarketing 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).

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
IMMUNOSUPPRESSANTS		
Immunosuppressants metabolized by CYP3A4 (eg, cyclosporine, 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.	Concomitant administration with efavirenz should be avoided due to the risk for QTc prolongation (see section 4.3).
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

There have been seven retrospective reports of findings consistent with neural tube defects, including meningomyelocele, 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 can not be excluded. Breast-feeding should be discontinued during treatment with SUSTIVA. 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

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.

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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); or very rare (< 1/10,000).

Immune system disorders	
uncommon	hypersensitivity
Metabolism and nutrition disorders	
common	hypertriglyceridaemia*
uncommon	hypercholesterolaemia*
Psychiatric disorders	
common	abnormal dreams, anxiety, depression, insomnia*
uncommon	affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, *psychosis*[†], suicide attempt, suicide ideation, catatonia*
rare	*delusion*[‡], *neurosis*[‡], *completed suicide*[‡,]*
Nervous system disorders	
common	*cerebellar coordination and balance disturbances*[†], disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%)*
uncommon	agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal,* *tremor*[†]
Eye disorders	
uncommon	vision blurred
Ear and labyrinth disorders	
uncommon	*tinnitus*[†], vertigo
Vascular disorders	
uncommon	*flushing*[†]
Gastrointestinal disorders	
common	abdominal pain, diarrhoea, nausea, vomiting
uncommon	pancreatitis

Hepatobiliary disorders	
common	aspartate aminotransferase (AST) increased*, alanine aminotransferase (ALT) increased*, gamma-glutamyltransferase (GGT) increased*
uncommon	hepatitis acute
rare	*hepatic failure*[‡,]*
Skin and subcutaneous tissue disorders	
very common	rash (11.6%)*
common	pruritus
uncommon	erythema multiforme, Stevens-Johnson syndrome*
rare	*photoallergic dermatitis*[†]
Reproductive system and breast disorders	
uncommon	gynaecomastia
General disorders and administration site conditions	
common	Fatigue

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

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 reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when efavirenz is restarted.

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. 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, psychosis-like behaviour and catatonia.

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 postmarketing 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 and autoimmune hepatitis) 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).

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.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Paediatric population

Undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (59 of 182 (32%) treated with efavirenz) and was more often of higher grade than in adults (severe rash was reported in 6 of 182 (3.3%) of children). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered. .

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: J05AG03

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).

Cardiac Electrophysiology

The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see section 4.5).

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/mm^3, 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-naive at study entry. The mean baseline CD4 cell count was 341 cells/mm^3 and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 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

		Responder rates (NC = F[a]) Plasma HIV-RNA		Mean change from baseline-CD4 cell count cells/mm^3 (S.E.M.[c])
		< 400 copies/ml (95% C.I.[b])	< 50 copies/ml (95% C.I.[b])	
Treatment Regimen[d]	n	48 weeks	48 weeks	48 weeks
EFV + ZDV + 3TC	202	67% (60%, 73%)	62% (55%, 69%)	187 (11.8)
EFV + IDV	206	54% (47%, 61%)	48% (41%, 55%)	177 (11.3)
IDV + ZDV + 3TC	206	45% (38%, 52%)	40% (34%, 47%)	153 (12.3)

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

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

Efficacy results for 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

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

Study AI266922 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in antiretroviral-naive and -experienced paediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with SUSTIVA. At baseline, median plasma HIV-1 RNA was 5.88 $\log_{10}$ copies/mL, median CD4+ cell count was 1144 cells/mm^3, and median CD4+ percentage was 25%. The median time on study therapy was 132 weeks; 27% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (21/37) and 46% (17/37), respectively. The median increase from baseline in CD4+ count at 48 weeks was 215 cells/mm^3 and the median increase in CD4+ percentage was 6%.

Study PACTG 1021 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in paediatric patients who were antiretroviral therapy naive. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with SUSTIVA. At baseline, median plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL, median CD4+ cell count was 367 cells/mm^3, and median CD4+ percentage was 18%. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 77% (33/43) and 70% (30/43), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 238 cells/mm^3 and the median increase in CD4+ percentage was 13%.

Study PACTG 382 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with nelfinavir and an NRTI in antiretroviral-naive and NRTI-experienced paediatric patients. One hundred two patients 3 months to 16 years of age (median 5.7 years) were treated with SUSTIVA. Eighty-seven percent of patients had received prior antiretroviral therapy. At baseline, median plasma HIV-1 RNA was 4.57 $\log_{10}$ copies/mL, median CD4+ cell count was 755 cells/mm^3, and median CD4+ percentage was 30%. The median time on study therapy was 118 weeks; 25% of patients discontinued before Week 48. Using an ITT analysis, the overall proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (58/102) and 43% (44/102), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 128 cells/mm^3 and the median increase in CD4+ percentage was 5%.

5.2 Pharmacokinetic properties

Absorption

Peak efavirenz plasma concentrations of 1.6 - 9.1 μM were attained by 5 hours following single oral doses of 100 mg to 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 μM (29%) [mean ± S.D. (% C.V.)], steady state C_{min} was 5.6 ± 3.2 μM (57%), and AUC was 184 ± 73 μM·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

*S*tudies 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

The pharmacokinetic parameters for efavirenz at steady state in paediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 4 by weight ranges that correspond to the recommended doses.

Table 4: Predicted steady-state pharmacokinetics of efavirenz (capsules/capsule sprinkles) in HIV-infected paediatric patients

Body Weight	Dose	Mean $AUC_{(0-24)}$ µM·h	Mean C_{max} µg/mL	Mean C_{min} µg/mL
3.5-5 kg	100 mg	220.52	5.81	2.43
5-7.5 kg	150 mg	262.62	7.07	2.71
7.5-10 kg	200 mg	284.28	7.75	2.87
10-15 kg	200 mg	238.14	6.54	2.32
15-20 kg	250 mg	233.98	6.47	2.3
20-25 kg	300 mg	257.56	7.04	2.55
25-32.5 kg	350 mg	262.37	7.12	2.68
32.5-40 kg	400 mg	259.79	6.96	2.69
>40 kg	600 mg	254.78	6.57	2.82

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, microophthalmia 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

Tablet core
Croscarmellose sodium
Microcrystalline cellulose
Sodium laurilsulfate
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate

Film coating
Hypromellose (E464)

Titanium dioxide (E171)
Macrogol 400
Yellow iron oxide (E172)
Carnauba wax

Printing ink
Hypromellose (E464)
Propylene glycol
Cochineal carminic acid (E120)
Indigo carmine (E132)
Titanium dioxide (E171)

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 content of container

HDPE bottles with a child-resistant polypropylene closure. Each carton contains 1 bottle of 30 film-coated tablets.
Packs of 30 x 1 or multipacks of 90 (3 packs of 30 x 1) film-coated tablets in aluminium/PVC perforated unit dose blisters.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG

Plaza 254
Blanchardstown Corporate Park 2
Dublin 15
D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/008 - bottle
EU/1/99/110/009 - blister
EU/1/99/110/010 - blister

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 May 1999
Date of latest renewal: 23 April 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
03012 Anagni (FR)
Italy

Aesica Queenborough Limited
North Road, Queenborough
Kent, ME11 5EL
United Kingdom

Aesica Pharmaceuticals GmbH - Monheim,
Alfred-Nobel-Straße 10,
40789 Monheim,
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL TEXT FOR BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 50 mg hard capsules
efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains: efavirenz 50 mg.

3. LIST OF EXCIPIENTS

It contains: lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

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

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15
D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUSTIVA 50 mg

17. UNIQUE IDENTIFIED – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIED – HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL TEXT FOR BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 100 mg hard capsules
efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains: efavirenz 100 mg.

3. LIST OF EXCIPIENTS

It contains: lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

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

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15
D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUSTIVA 100 mg

17. UNIQUE IDENTIFIED – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIED – HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL TEXT FOR BOTTLE PACK
OUTER CARTON TEXT FOR BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 200 mg hard capsules
efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains: efavirenz 200 mg

3. LIST OF EXCIPIENTS

It contains: lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

90 hard capsules: bottle
42 x 1 hard capsules: blister

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

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

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15
D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/003: bottle
EU/1/99/110/004: blister

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUSTIVA 200 mg

17. UNIQUE IDENTIFIED – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIED – HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 200 mg hard capsules
efavirenz

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL TEXT FOR BOTTLE PACK
OUTER CARTON TEXT FOR BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 600 mg film-coated tablets
efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: efavirenz 600 mg.

3. LIST OF EXCIPIENTS

It contains: lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Bottle:
30 film-coated tablets

Blister:
30 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

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

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15
D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

Bottle:
EU/1/99/110/008

Blister:
EU/1/99/110/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUSTIVA 600 mg

17. UNIQUE IDENTIFIED – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIED – HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT FOR BLISTER MULTIPACK (INCLUDING BLUE-BOX)

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 600 mg film-coated tablets
efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: efavirenz 600 mg.

3. LIST OF EXCIPIENTS

It 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

Read the package leaflet before use.
Oral 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

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

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15
D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUSTIVA 600 mg

17. UNIQUE IDENTIFIED – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIED – HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

PARTICULARS TO APPEAR ON OUTER PACKAGING

CARTON TEXT FOR BLISTER INTERMEDIATE PACK, COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)
30 x 1 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 600 mg film-coated tablets
efavirenz

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: efavirenz 600 mg.

3. LIST OF EXCIPIENTS

It 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

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

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15
D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUSTIVA 600 mg

17. UNIQUE IDENTIFIED – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIED – HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 600 mg film-coated tablet
efavirenz

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

SUSTIVA 50 mg hard capsules
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 side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SUSTIVA is and what it is used for

SUSTIVA, 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 months of age and older and weighing at least 3.5 kg.
Your doctor has prescribed SUSTIVA for you because you have HIV infection.
SUSTIVA 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 SUSTIVA

Do not take SUSTIVA
- **if you are allergic** 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 have a heart condition, such as changes in the rhythm or rate of the heart beat, a slow heart beat, or severe heart disease.**

- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due to a heart problem or was born with heart problems.

- if your doctor has told you that you have high or low levels of electrolytes such as potassium or magnesium in your blood.

- **if you are currently taking** any of the following medicines (see also "Other medicines and Sustiva"):
  - **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, imipramine, amitriptyline or clomipramine** (used to treat certain mental conditions)
- **elbasvir or grazoprevir** (used to treat hepatitis C)
- **St. John's wort** (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)
- **flecainide, metoprolol** (used to treat irregular heart beat)
- **certain antibiotics** (macrolides, fluoroquinolones, imidazole)
- **triazole antifungal agents**
- certain **antimalarial treatments**
- **methadone** (used to treat opiate addiction)

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with SUSTIVA could create the potential for serious and/or life-threatening side-effects or stop SUSTIVA from working properly.

Warnings and precautions
Talk to your doctor before taking SUSTIVA

- **SUSTIVA must be taken with other medicines that act against the HIV virus.** If SUSTIVA 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 SUSTIVA.

- **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 SUSTIVA. 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 SUSTIVA** (see section 2, *Do not take SUSTIVA*).

  - **if you have a heart disorder, such as abnormal electrical signal called prolongation of the QT interval.**

- **Once you start taking SUSTIVA, 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 SUSTIVA 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 SUSTIVA.

- **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.

- **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
SUSTIVA is not recommeded for children under the age of 3 months or weighing less than 3.5 kg because it has not been adequately studied in these patients.

Other medicines and SUSTIVA
You must not take SUSTIVA with certain medicines. These are listed under Do not take SUSTIVA, 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.

SUSTIVA may interact with other medicines, including herbal preparations such as *Ginkgo biloba* extracts. As a result, the amounts of SUSTIVA 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 SUSTIVA unless recommended by your doctor since it contains efavirenz, the active ingredient of SUSTIVA.

- **Medicines used to treat infection with the hepatitis C virus:** boceprevir, telaprevir, elbasvir/grazoprevir, simeprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, glecaprevir/pibrentasvir.

- **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 SUSTIVA.

- **Medicines used to treat fungal infections (antifungals):**
  - voriconazole. SUSTIVA may reduce the amount of voriconazole in your blood and voriconazole may increase the amount of SUSTIVA 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. SUSTIVA may reduce the amount of itraconazole in your blood.
  - posaconazole. SUSTIVA may reduce the amount of posaconazole in your blood.

- **Medicines used to treat malaria:**
  - artemether/lumefantrine: SUSTIVA may reduce the amount of artemether/lumefantrine in your blood.
  - atovaquone/proguanil: SUSTIVA may reduce the amount of atovaquone/proguanil in your blood.

- **Medicines used to treat convulsions/seizures (anticonvulsants):** carbamazepine, phenytoin, phenobarbital. SUSTIVA can reduce or increase the amount of anticonvulsant in your blood. Carbamazepine may make SUSTIVA 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. SUSTIVA 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 recommend an alternative treatment.

- **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 SUSTIVA, your doctor may need to adjust your dose of the calcium channel blocker.

- **Immunosuppressants such as cyclosporine, sirolimus, or tacrolimus** (medicines used to prevent organ transplant rejection)**:** when you start or stop taking SUSTIVA, 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). SUSTIVA may make hormonal contraceptives less likely to work. Pregnancies have occurred in women taking SUSTIVA while using a contraceptive implant, although it has not been established that the SUSTIVA 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)

- **Medicines that impact heart rhythm:**
  - **Medicines used to treat heart rhythm problems:** such as flecainide or metoprolol.
  - **Medicines used to treat depression** such as imipramine, amitriptyline or clomipramine
  - **Antibiotics**, including the following types: macrolides, fluoroquinolones or imidazole.

SUSTIVA with food and drink
Taking SUSTIVA on an empty stomach may reduce the undesirable effects. Grapefuit juice should be avoided when taking SUSTIVA.

Pregnancy and breast-feeding
Women should not get pregnant during treatment with SUSTIVA, 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 SUSTIVA.

If you could get pregnant while receiving SUSTIVA, 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 SUSTIVA.

Tell your doctor immediately if you are pregnant or intend to become pregnant. If you are pregnant, you should take SUSTIVA 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 SUSTIVA 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 SUSTIVA.

Driving and using machines
SUSTIVA 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.

SUSTIVA contains lactose 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.

3. How to take SUSTIVA

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 SUSTIVA may need to be increased or decreased if you are also taking certain medicines (see Other medicines and SUSTIVA).

- SUSTIVA is for oral use. SUSTIVA 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 capsule be swallowed whole with water.
- SUSTIVA must be taken every day.
- SUSTIVA should never be used alone to treat HIV. SUSTIVA must always be taken in combination with other anti-HIV medicines.

Use in children and adolescents

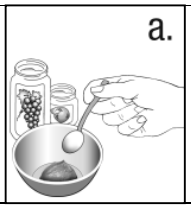
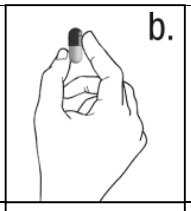
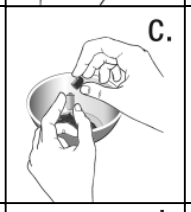
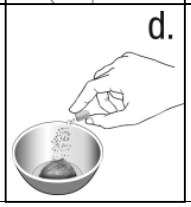
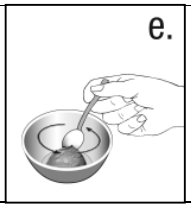
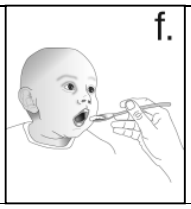
- SUSTIVA 50 mg hard capsules can be taken by children and adolescents 3 months of age and older and weighing at least 3.5 kg who are able to swallow the capsules. Opening the capsule and taking the contents with a small amount of food may be considered for children who cannot swallow the hard capsule.
- The dose for children and adolescents is calculated by body weight and is taken once daily as shown below:

Body Weight **kg**	**SUSTIVA** **Dose (mg)**	**Number of Capsules or Tablets and Strength to Administer**
3.5 to < 5	100	one 100 mg capsule
5 to < 7.5	150	one 100 mg capsule + one 50 mg capsule
7.5 to < 15	200	one 200 mg capsule
15 to < 20	250	one 200 mg capsule + one 50 mg capsule
20 to < 25	300	three 100 mg capsules
25 to < 32.5	350	three 100 mg capsules + one 50 mg capsule
32.5 to < 40	400	two 200 mg capsules
≥ 40	600	one 600 mg tablet OR three 200 mg capsules

For children who are not able to swallow the capsules, the doctor may recommend opening the hard capsule and mixing the contents with a small amount (1-2 teaspoons) of food (e.g., yogurt). The capsules must be opened carefully so that the contents do not spill or escape into the air. Hold the capsule with the cap facing up and pull the cap away from the body of the capsule. Use a small container for mixing. Give the mixture to the child as soon as possible, but no more than 30 minutes after mixing. Make sure the child eats the full amount of the mixture of food and capsule contents. Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container, stirring to make sure there is no drug residue remaining in the container, and have the child eat the full amount again. The child should not be given any additional food for 2 hours. The doctor may also recommend this method of taking SUSTIVA for adults who cannot swallow capsules.

Instructions for capsule sprinkle method:

1	Avoid giving the daily SUSTIVA dose within 1 hour after a feeding or meal.
2	Wash and dry your hands before and after preparing the capsule sprinkle.
3	Choose a soft food the child likes. Examples of soft foods are applesauce, grape jelly, yogurt, or infant formula. In a taste preference study in adults, SUSTIVA mixed with grape jelly received the best rating.

4	Place 1-2 teaspoons of the food in a small container (illustration a).	 a.
5	**SUSTIVA capsules must be opened carefully over the food container**, as described in steps 6-7, **so that the contents do not spill**.	
6	With your hands over the container, hold the capsule with the cap facing up (see illustration b).	 b.
7	Carefully pull the cap away from the body of the capsule (illustration c).	 c.
8	Sprinkle the contents of the capsule on the food (illustration d).	 d.
9	If the daily dose consists of more than one capsule, follow steps 5-8 for each capsule. **Do not** add more food.	
10	Mix the capsule contents and food together (illustration e).	 e.
Steps 11-14 must be completed within 30 minutes of mixing:		
11	Give the mixture of food and capsule contents to the child, making sure he or she eats the full amount (illustration f).	 f.
12	Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container (illustration a).	
13	Stir to make sure there is no drug residue remaining in the container (illustration e).	
14	Have the child eat the full amount again (illustration f).	
15	**Do not give the child any additional food for 2 hours.**	

If you take more SUSTIVA than you should
If you take too much SUSTIVA 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 SUSTIVA
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 SUSTIVA
When your SUSTIVA 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 SUSTIVA or by other medicines that you are taking at the same time, or by the HIV disease itself.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

The most notable unwanted effects reported with SUSTIVA 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 SUSTIVA. Rash was more common in children than in adults treated with SUSTIVA.

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 SUSTIVA 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 SUSTIVA.

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 coordination 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 trigycerides (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, catatonia (condition in which the patient is rendered motionless and speechless for a period)
- 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

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 SUSTIVA

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 bottle 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 SUSTIVA contains

- Each SUSTIVA hard capsule contains 50 mg of the active substance efavirenz.
- The other ingredients of the powder contained in the hard capsule are: sodium laurilsulfate, lactose monohydrate, magnesium stearate and sodium starch glycolate.
- The capsule shell contains: gelatine, sodium laurilsulfate, yellow iron oxide (E172), titanium dioxide (E171) and silicon dioxide.
- The capsules are printed with inks containing cochineal carminic acid (E120), indigo carmine (E132), and titanium dioxide (E171).

What SUSTIVA looks like and contents of the pack
SUSTIVA 50 mg hard capsules are supplied in bottles of 30 capsules.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

SUSTIVA 100 mg hard capsules
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 side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SUSTIVA is and what it is used for

SUSTIVA, 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 months of age and older and weighing at least 3.5 kg.
Your doctor has prescribed SUSTIVA for you because you have HIV infection.
SUSTIVA 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 SUSTIVA

Do not take SUSTIVA
- **if you are allergic** 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 have a heart condition, such as changes in the rhythm or rate of the heart beat, a slow heart beat, or severe heart disease.**

- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due to a heart problem or was born with heart problems.

- if your doctor has told you that you have high or low levels of electrolytes such as potassium or magnesium in your blood.

- **if you are currently taking** any of the following medicines(see also “Other medicines and Sustiva”):
  - **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, imipramine, amitriptyline or clomipramine** (used to treat certain mental conditions)
- **elbasvir or grazoprevir** (used to treat hepatitis C)
- **St. John's wort** (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)
- **flecainide, metoprolol** (used to treat irregular heart beat)
- **certain antibiotics** (macrolides, fluoroquinolones, imidazole)
- **triazole antifungal agents**
- certain **antimalarial treatments**
- **methadone** (used to treat opiate addiction)

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with SUSTIVA could create the potential for serious and/or life-threatening side-effects or stop SUSTIVA from working properly.

Warnings and precautions
Talk to your doctor before taking SUSTIVA

- **SUSTIVA must be taken with other medicines that act against the HIV virus.** If SUSTIVA 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 SUSTIVA.

- **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 SUSTIVA. 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 SUSTIVA** (see section 2, *Do not take SUSTIVA*).

  - **if you have a heart disorder, such as abnormal electrical signal called prolongation of the QT interval.**

- **Once you start taking SUSTIVA, 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 SUSTIVA 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 SUSTIVA.

  - **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.

  - **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
SUSTIVA is not recommeded for children under the age of 3 months or weighing less than 3.5 kg because it has not been adequately studied in these patients.

Other medicines and SUSTIVA
You must not take SUSTIVA with certain medicines. These are listed under Do not take SUSTIVA, 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.

SUSTIVA may interact with other medicines, including herbal preparations such as *Ginkgo biloba* extracts. As a result, the amounts of SUSTIVA 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 SUSTIVA unless recommended by your doctor since it contains efavirenz, the active ingredient of SUSTIVA.

- **Medicines used to treat infection with the hepatitis C virus:** boceprevir, telaprevir, elbasvir/grazoprevir, simeprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, glecaprevir/pibrentasvir.

- **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 SUSTIVA.

- **Medicines used to treat fungal infections (antifungals):**
  - voriconazole. SUSTIVA may reduce the amount of voriconazole in your blood and voriconazole may increase the amount of SUSTIVA 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. SUSTIVA may reduce the amount of itraconazole in your blood.
  - posaconazole. SUSTIVA may reduce the amount of posaconazole in your blood.

- **Medicines used to treat malaria:**
  - artemether/lumefantrine: SUSTIVA may reduce the amount of artemether/lumefantrine in your blood.
  - atovaquone/proguanil: SUSTIVA may reduce the amount of atovaquone/proguanil in your blood.

- **Medicines used to treat convulsions/seizures (anticonvulsants):** carbamazepine, phenytoin, phenobarbital. SUSTIVA can reduce or increase the amount of anticonvulsant in your blood. Carbamazepine may make SUSTIVA 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. SUSTIVA 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 recommend an alternative treatment.

- **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 SUSTIVA, your doctor may need to adjust your dose of the calcium channel blocker.

- **Immunosuppressants such as cyclosporine, sirolimus, or tacrolimus** (medicines used to prevent organ transplant rejection)**:** when you start or stop taking SUSTIVA, 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). SUSTIVA may make hormonal contraceptives less likely to work. Pregnancies have occurred in

women taking SUSTIVA while using a contraceptive implant, although it has not been established that the SUSTIVA 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)

- **Medicines that impact heart rhythm:**
  - **Medicines used to treat heart rhythm problems** such as flecainide or metoprolol.
  - **Medicines used to treat depression** such as imipramine, amitriptyline or clomipramine.
  - **Antibiotics**, including the following types: macrolides, fluoroquinolones or imidazole.

SUSTIVA with food and drink
Taking SUSTIVA on an empty stomach may reduce the undesirable effects. Grapefuit juice should be avoided when taking SUSTIVA.

Pregnancy and breast-feeding
Women should not get pregnant during treatment with SUSTIVA, 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 SUSTIVA.

If you could get pregnant while receiving SUSTIVA, 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 SUSTIVA.

Tell your doctor immediately if you are pregnant or intend to become pregnant. If you are pregnant, you should take SUSTIVA 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 SUSTIVA 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 SUSTIVA.

Driving and using machines
SUSTIVA 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.

SUSTIVA contains lactose 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.

3. How to take SUSTIVA

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 SUSTIVA may need to be increased or decreased if you are also taking certain medicines (see Other medicines and SUSTIVA).
- SUSTIVA is for oral use. SUSTIVA 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 capsule be swallowed whole with water.
- SUSTIVA must be taken every day.
- SUSTIVA should never be used alone to treat HIV. SUSTIVA must always be taken in combination with other anti-HIV medicines.

Use in children and adolescents

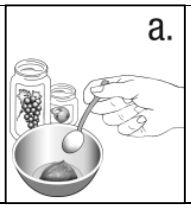
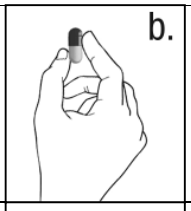
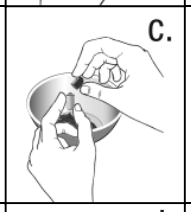
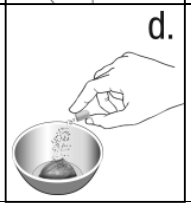
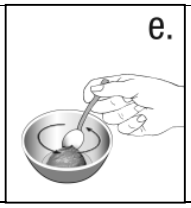
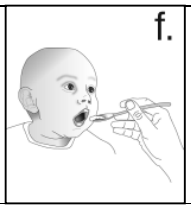
- SUSTIVA 100 mg hard capsules can be taken by children and adolescents 3 months of age and older and weighing at least 3.5 kg who are able to swallow the capsules. Opening the capsule and taking the contents with a small amount of food may be considered for children who cannot swallow the hard capsule.
- The dose for children and adolescents is calculated by body weight and is taken once daily as shown below:

Body Weight **kg**	**SUSTIVA** **Dose (mg)**	**Number of Capsules or Tablets and Strength to Administer**
3.5 to < 5	100	one 100 mg capsule
5 to < 7.5	150	one 100 mg capsule + one 50 mg capsule
7.5 to < 15	200	one 200 mg capsule
15 to < 20	250	one 200 mg capsule + one 50 mg capsule
20 to < 25	300	three 100 mg capsules
25 to < 32.5	350	three 100 mg capsules + one 50 mg capsule
32.5 to < 40	400	two 200 mg capsules
≥ 40	600	one 600 mg tablet OR three 200 mg capsules

For children who are not able to swallow the capsules, the doctor may recommend opening the hard capsule and mixing the contents with a small amount (1-2 teaspoons) of food (e.g., yogurt). The capsules must be opened carefully so that the contents do not spill or escape into the air. Hold the capsule with the cap facing up and pull the cap away from the body of the capsule. Use a small container for mixing. Give the mixture to the child as soon as possible, but no more than 30 minutes after mixing. Make sure the child eats the full amount of the mixture of food and capsule contents. Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container, stirring to make sure there is no drug residue remaining in the container, and have the child eat the full amount again. The child should not be given any additional food for 2 hours. The doctor may also recommend this method of taking SUSTIVA for adults who cannot swallow capsules.

Instructions for capsule sprinkle method:

1	Avoid giving the daily SUSTIVA dose within 1 hour after a feeding or meal.
2	Wash and dry your hands before and after preparing the capsule sprinkle.
3	Choose a soft food the child likes. Examples of soft foods are applesauce, grape jelly, yogurt, or infant formula. In a taste preference study in adults, SUSTIVA mixed with grape jelly received the best rating.

4	Place 1-2 teaspoons of the food in a small container (illustration a).	 a.
5	**SUSTIVA capsules must be opened carefully over the food container**, as described in steps 6-7, **so that the contents do not spill**.	
6	With your hands over the container, hold the capsule with the cap facing up (see illustration b).	 b.
7	Carefully pull the cap away from the body of the capsule (illustration c).	 c.
8	Sprinkle the contents of the capsule on the food (illustration d).	 d.
9	If the daily dose consists of more than one capsule, follow steps 5-8 for each capsule. **Do not** add more food.	
10	Mix the capsule contents and food together (illustration e).	 e.
Steps 11-14 must be completed within 30 minutes of mixing:		
11	Give the mixture of food and capsule contents to the child, making sure he or she eats the full amount (illustration f).	 f.
12	Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container (illustration a).	
13	Stir to make sure there is no drug residue remaining in the container (illustration e).	
14	Have the child eat the full amount again (illustration f).	
15	**Do not give the child any additional food for 2 hours.**	

If you take more SUSTIVA than you should
If you take too much SUSTIVA 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 SUSTIVA
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 SUSTIVA
When your SUSTIVA 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 SUSTIVA or by other medicines that you are taking at the same time, or by the HIV disease itself.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

The most notable unwanted effects reported with SUSTIVA 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 SUSTIVA. Rash was more common in children than in adults treated with SUSTIVA.

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 SUSTIVA 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 SUSTIVA.

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 coordination 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 trigycerides (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, catatonia (condition in which the patient is rendered motionless and speechless for a period)
- 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

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 SUSTIVA

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 bottle 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 SUSTIVA contains

- Each SUSTIVA hard capsule contains 100 mg of the active substance efavirenz.
- The other ingredients of the powder contained in the hard capsule are: sodium laurilsulfate, lactose monohydrate, magnesium stearate and sodium starch glycolate.
- The capsule shell contains: gelatine, sodium laurilsulfate, titanium dioxide (E171) and silicon dioxide.
- The capsules are printed with inks containing cochineal carminic acid (E120), indigo carmine (E132), and titanium dioxide (E171).

What SUSTIVA looks like and contents of the pack
SUSTIVA 100 mg hard capsules are supplied in bottles of 30 capsules.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

SUSTIVA 200 mg hard capsules
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 side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SUSTIVA is and what it is used for

SUSTIVA, 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 months of age and older and weighing at least 3.5 kg.
Your doctor has prescribed SUSTIVA for you because you have HIV infection.
SUSTIVA 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 SUSTIVA

Do not take SUSTIVA
- **if you are allergic** 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 have a heart condition, such as changes in the rhythm or rate of the heart beat, a slow heart beat, or severe heart disease.**

- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due to a heart problem or was born with heart problems.

- if your doctor has told you that you have high or low levels of electrolytes such as potassium or magnesium in your blood.

- **if you are currently taking** any of the following medicines (see also "Other medicines and Sustiva"):
  - **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, imipramine, amitriptyline or clomipramine** (used to treat certain mental conditions)
- **elbasvir or grazoprevir** (used to treat hepatitis C)
- **St. John's wort** (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)
- **flecainide, metoprolol** (used to treat irregular heart beat)
- **certain antibiotics** (macrolides, fluoroquinolones, imidazole)
- **triazole antifungal agents**
- certain **antimalarial treatments**
- **methadone** (used to treat opiate addiction)

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with SUSTIVA could create the potential for serious and/or life-threatening side-effects or stop SUSTIVA from working properly.

Warnings and precautions
Talk to your doctor before taking SUSTIVA

- **SUSTIVA must be taken with other medicines that act against the HIV virus.** If SUSTIVA 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 SUSTIVA.

- **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 SUSTIVA. 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 SUSTIVA** (see section 2, *Do not take SUSTIVA*).

  - **if you have a heart disorder, such as abnormal electrical signal called prolongation of the QT interval.**

- **Once you start taking SUSTIVA, 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 SUSTIVA 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 SUSTIVA.

  - **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.

  - **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
SUSTIVA is not recommeded for children under the age of 3 months or weighing less than 3.5 kg because it has not been adequately studied in these patients.

Other medicines and SUSTIVA
You must not take SUSTIVA with certain medicines. These are listed under Do not take SUSTIVA, 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.

SUSTIVA may interact with other medicines, including herbal preparations such as *Ginkgo biloba* extracts. As a result, the amounts of SUSTIVA 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 SUSTIVA unless recommended by your doctor since it contains efavirenz, the active ingredient of SUSTIVA.

- **Medicines used to treat infection with the hepatitis C virus:** boceprevir, telaprevir, elbasvir/grazoprevir, simeprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, glecaprevir/pibrentasvir.

- **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 SUSTIVA.

- **Medicines used to treat fungal infections (antifungals):**
  - voriconazole. SUSTIVA may reduce the amount of voriconazole in your blood and voriconazole may increase the amount of SUSTIVA 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. SUSTIVA may reduce the amount of itraconazole in your blood.
  - posaconazole. SUSTIVA may reduce the amount of posaconazole in your blood.

- **Medicines used to treat malaria:**
  - artemether/lumefantrine: SUSTIVA may reduce the amount of artemether/lumefantrine in your blood.
  - atovaquone/proguanil: SUSTIVA may reduce the amount of atovaquone/proguanil in your blood.

- **Medicines used to treat convulsions/seizures (anticonvulsants):** carbamazepine, phenytoin, phenobarbital. SUSTIVA can reduce or increase the amount of anticonvulsant in your blood. Carbamazepine may make SUSTIVA 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. SUSTIVA 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 recommend an alternative treatment.

- **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 SUSTIVA, your doctor may need to adjust your dose of the calcium channel blocker.

- **Immunosuppressants such as cyclosporine, sirolimus, or tacrolimus** (medicines used to prevent organ transplant rejection)**:** when you start or stop taking SUSTIVA, 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). SUSTIVA may make hormonal contraceptives less likely to work. Pregnancies have occurred in

women taking SUSTIVA while using a contraceptive implant, although it has not been established that the SUSTIVA 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)

- **Medicines that impact heart rhythm:**
  - **Medicines used to treat heart rhythm problems** such as flecainide or metoprolol.
  - **Medicines used to treat depression** such as imipramine, amitriptyline or clomipramine.
  - **Antibiotics**, including the following types: macrolides, fluoroquinolones or imidazole.

SUSTIVA with food and drink
Taking SUSTIVA on an empty stomach may reduce the undesirable effects. Grapefuit juice should be avoided when taking SUSTIVA.

Pregnancy and breast-feeding
Women should not get pregnant during treatment with SUSTIVA, 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 SUSTIVA.

If you could get pregnant while receiving SUSTIVA, 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 SUSTIVA.

Tell your doctor immediately if you are pregnant or intend to become pregnant. If you are pregnant, you should take SUSTIVA 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 SUSTIVA 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 SUSTIVA.

Driving and using machines
SUSTIVA 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.

SUSTIVA contains lactose 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.

3. How to take SUSTIVA

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 SUSTIVA may need to be increased or decreased if you are also taking certain medicines (see Other medicines and SUSTIVA).
- SUSTIVA is for oral use. SUSTIVA 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 capsule be swallowed whole with water.
- SUSTIVA must be taken every day.
- SUSTIVA should never be used alone to treat HIV. SUSTIVA must always be taken in combination with other anti-HIV medicines.

Use in children and adolescents

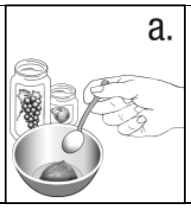
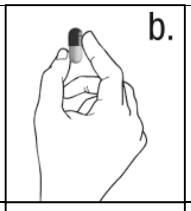
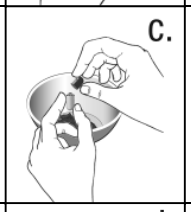
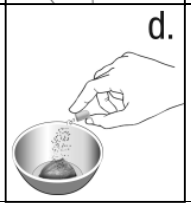
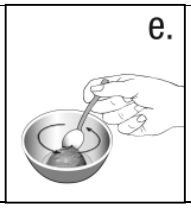
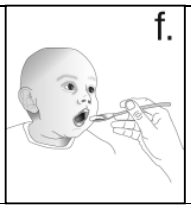
- SUSTIVA 200 mg hard capsules can be taken by children and adolescents 3 months of age and older and weighing at least 3.5 kg who are able to swallow the capsules. Opening the capsule and taking the contents with a small amount of food may be considered for children who cannot swallow the hard capsule.
- The dose for children and adolescents is calculated by body weight and is taken once daily as shown below:

Body Weight **kg**	**SUSTIVA** **Dose (mg)**	**Number of Capsules or Tablets and Strength to Administer**
3.5 to < 5	100	one 100 mg capsule
5 to < 7.5	150	one 100 mg capsule + one 50 mg capsule
7.5 to < 15	200	one 200 mg capsule
15 to < 20	250	one 200 mg capsule + one 50 mg capsule
20 to < 25	300	three 100 mg capsules
25 to < 32.5	350	three 100 mg capsules + one 50 mg capsule
32.5 to < 40	400	two 200 mg capsules
≥ 40	600	one 600 mg tablet OR three 200 mg capsules

For children who are not able to swallow the capsules, the doctor may recommend opening the hard capsule and mixing the contents with a small amount (1-2 teaspoons) of food (e.g., yogurt). The capsules must be opened carefully so that the contents do not spill or escape into the air. Hold the capsule with the cap facing up and pull the cap away from the body of the capsule. Use a small container for mixing. Give the mixture to the child as soon as possible, but no more than 30 minutes after mixing. Make sure the child eats the full amount of the mixture of food and capsule contents. Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container, stirring to make sure there is no drug residue remaining in the container, and have the child eat the full amount again. The child should not be given any additional food for 2 hours. The doctor may also recommend this method of taking SUSTIVA for adults who cannot swallow capsules.

Instructions for capsule sprinkle method:

1	Avoid giving the daily SUSTIVA dose within 1 hour after a feeding or meal.
2	Wash and dry your hands before and after preparing the capsule sprinkle.
3	Choose a soft food the child likes. Examples of soft foods are applesauce, grape jelly, yogurt, or infant formula. In a taste preference study in adults, SUSTIVA mixed with grape jelly received the best rating.

4	Place 1-2 teaspoons of the food in a small container (illustration a).	 a.
5	**SUSTIVA capsules must be opened carefully over the food container**, as described in steps 6-7, **so that the contents do not spill**.	
6	With your hands over the container, hold the capsule with the cap facing up (see illustration b).	 b.
7	Carefully pull the cap away from the body of the capsule (illustration c).	 c.
8	Sprinkle the contents of the capsule on the food (illustration d).	 d.
9	If the daily dose consists of more than one capsule, follow steps 5-8 for each capsule. **Do not** add more food.	
10	Mix the capsule contents and food together (illustration e).	 e.
Steps 11-14 must be completed within 30 minutes of mixing:		
11	Give the mixture of food and capsule contents to the child, making sure he or she eats the full amount (illustration f).	 f.
12	Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container (illustration a).	
13	Stir to make sure there is no drug residue remaining in the container (illustration e).	
14	Have the child eat the full amount again (illustration f).	
15	**Do not give the child any additional food for 2 hours.**	

If you take more SUSTIVA than you should
If you take too much SUSTIVA 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 SUSTIVA
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 SUSTIVA
When your SUSTIVA 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 SUSTIVA or by other medicines that you are taking at the same time, or by the HIV disease itself.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

The most notable unwanted effects reported with SUSTIVA 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 SUSTIVA. Rash was more common in children than in adults treated with SUSTIVA.

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 SUSTIVA 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 SUSTIVA.

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 coordination 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 trigycerides (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, catatonia (condition in which the patient is rendered motionless and speechless for a period)
- 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

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 SUSTIVA

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 bottle or 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 SUSTIVA contains

- Each SUSTIVA hard capsule contains 200 mg of the active substance efavirenz.
- The other ingredients of the powder contained in the hard capsule are: sodium laurilsulfate, lactose monohydrate, magnesium stearate and sodium starch glycolate.
- The capsule shell contains: gelatine, sodium laurilsulfate, yellow iron oxide (E172) and silicon dioxide.
- The capsules are printed with inks containing cochineal carminic acid (E120), indigo carmine (E132), and titanium dioxide (E171).

What SUSTIVA looks like and contents of the pack
SUSTIVA 200 mg hard capsules are supplied in bottles of 90 capsules and in packs containing 42 x 1 capsules in aluminium/PVC perforated unit dose blisters. Not all pack sizes may be marketed.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

SUSTIVA 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 side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SUSTIVA is and what it is used for

SUSTIVA, 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 months of age and older and weighing at least 3.5 kg.
Your doctor has prescribed SUSTIVA for you because you have HIV infection.
SUSTIVA 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 SUSTIVA

Do not take SUSTIVA
- **if you are allergic** 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 have a heart condition, such as changes in the rhythm or rate of the heart beat, a slow heart beat, or severe heart disease.**

- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due to a heart problem or was born with heart problems.

- if your doctor has told you that you have high or low levels of electrolytes such as potassium or magnesium in your blood.

- **if you are currently taking** any of the following medicines (see also "Other medicines and Sustiva"):
  - **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, imipramine, amitriptyline or clomipramine** (used to treat certain mental conditions)
- **elbasvir or grazoprevir** (used to treat hepatitis C)
- **St. John's wort** (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)
- **flecainide, metoprolol** (used to treat irregular heart beat)
- **certain antibiotics** (macrolides, fluoroquinolones, imidazole)
- **triazole antifungal agents**
- certain **antimalarial treatments**
- **methadone** (used to treat opiate addiction)

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with SUSTIVA could create the potential for serious and/or life-threatening side-effects or stop SUSTIVA from working properly.

Warnings and precautions
Talk to your doctor before taking SUSTIVA

- **SUSTIVA must be taken with other medicines that act against the HIV virus.** If SUSTIVA 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 SUSTIVA.

- **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 SUSTIVA. 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 SUSTIVA** (see section 2, *Do not take SUSTIVA*).

  - **if you have a heart disorder, such as abnormal electrical signal called prolongation of the QT interval.**

- **Once you start taking SUSTIVA, 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 SUSTIVA 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 SUSTIVA.

- **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.

- **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
SUSTIVA is not recommeded for children under the age of 3 months or weighing less than 3.5 kg because it has not been adequately studied in these patients

Other medicines and SUSTIVA
You must not take SUSTIVA with certain medicines. These are listed under Do not take SUSTIVA, 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.

SUSTIVA may interact with other medicines, including herbal preparations such as *Ginkgo biloba* extracts. As a result, the amounts of SUSTIVA 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 SUSTIVA unless recommended by your doctor since it contains efavirenz, the active ingredient of SUSTIVA.

- **Medicines used to treat infection with the hepatitis C virus:** boceprevir, telaprevir, elbasvir/grazoprevir, simeprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, glecaprevir/pibrentasvir.

- **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 SUSTIVA.

- **Medicines used to treat fungal infections (antifungals):**
  - voriconazole. SUSTIVA may reduce the amount of voriconazole in your blood and voriconazole may increase the amount of SUSTIVA 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. SUSTIVA may reduce the amount of itraconazole in your blood.
  - posaconazole. SUSTIVA may reduce the amount of posaconazole in your blood.

- **Medicines used to treat malaria:**
  - artemether/lumefantrine: SUSTIVA may reduce the amount of artemether/lumefantrine in your blood.
  - atovaquone/proguanil: SUSTIVA may reduce the amount of atovaquone/proguanil in your blood.

- **Medicines used to treat convulsions/seizures (anticonvulsants):** carbamazepine, phenytoin, phenobarbital. SUSTIVA can reduce or increase the amount of anticonvulsant in your blood. Carbamazepine may make SUSTIVA 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. SUSTIVA 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 recommend an alternative treatment.

- **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 SUSTIVA, your doctor may need to adjust your dose of the calcium channel blocker.

- **Immunosuppressants such as cyclosporine, sirolimus, or tacrolimus** (medicines used to prevent organ transplant rejection): when you start or stop taking SUSTIVA, 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). SUSTIVA may make hormonal contraceptives less likely to work. Pregnancies have occurred in women taking SUSTIVA while using a contraceptive implant, although it has not been established that the SUSTIVA 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)

- **Medicines that impact heart rhythm:**
  - **Medicines used to treat heart rhythm problems** such as flecainide or metoprolol.
  - **Medicines used to treat depression** such as imipramine, amitriptyline or clomipramine.
  - **Antibiotics**, including the following types: macrolides, fluoroquinolones or imidazole.

SUSTIVA with food and drink
Taking SUSTIVA on an empty stomach may reduce the undesirable effects. Grapefuit juice should be avoided when taking SUSTIVA.

Pregnancy and breast-feeding
Women should not get pregnant during treatment with SUSTIVA 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 SUSTIVA.

If you could get pregnant while receiving SUSTIVA, 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 SUSTIVA.

Tell your doctor immediately if you are pregnant or intend to become pregnant. If you are pregnant, you should take SUSTIVA 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 SUSTIVA 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 SUSTIVA.

Driving and using machines
SUSTIVA 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.

SUSTIVA contains lactose 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.

3. How to take SUSTIVA

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 SUSTIVA may need to be increased or decreased if you are also taking certain medicines (see Other medicines and SUSTIVA).

- SUSTIVA is for oral use. SUSTIVA 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.
- SUSTIVA must be taken every day.
- SUSTIVA should never be used alone to treat HIV. SUSTIVA must always be taken in combination with other anti-HIV medicines.

Use in children and adolescents
- SUSTIVA 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 SUSTIVA than you should
If you take too much SUSTIVA, 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 SUSTIVA
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 SUSTIVA
When your SUSTIVA 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 SUSTIVA or by other medicines that you are taking at the same time, or by the HIV disease itself.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

The most notable unwanted effects reported with SUSTIVA 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 SUSTIVA. Rash was more common in children than in adults treated with SUSTIVA.

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 SUSTIVA 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 SUSTIVA.

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 coordination 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 trigycerides (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, catatonia (condition in which the patient is rendered motionless and speechless for a period)
- 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

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 SUSTIVA

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 bottle or 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. FURTHER INFORMATION

What SUSTIVA contains

- Each SUSTIVA film-coated tablet contains 600 mg of the active substance efavirenz.
- The other ingredients of the tablet core are: croscarmellose sodium, microcrystalline cellulose, sodium laurilsulfate, hydroxypropylcellulose, lactose monohydrate, and magnesium stearate.
- The film coating contains: hypromellose (E464), titanium dioxide (E171), macrogol 400, yellow iron oxide (E172) and carnauba wax.
- The tablets are printed with inks containing hypromellose (E464), propylene glycol, cochineal carminic acid (E120), indigo carmine (E132) and titanium dioxide (E171).

What SUSTIVA looks like and contents of the pack
SUSTIVA 600 mg film-coated tablets are supplied in bottles of 30 tablets.
SUSTIVA 600 mg film-coated tablets are also supplied in packs containing 30 x 1 or multipacks of 90 (3 packs of 30 x 1) tablets in aluminium/PVC perforated unit dose blisters. Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for efavirenz, the scientific conclusions of CHMP are as follows:

For the drug-drug interaction with etonogestrel implant, the PRAC noted the available data from 16 case reports and the published literature articles by Vieira et al., 2014 and Chappel et al., 2017. Based on this new data, the PRAC considers that the statement that the interaction between etonogestrel and efavirenz has not been studied is no longer valid and that this statement should be removed from the SmPC of all efavirenz-containing products.

In view of the data presented in the reviewed PSUR, the overall risk-benefit balance of efavirenz is therefore considered unchanged in the approved indications provided that the terms of the marketing authorisation are varied as relevant.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for efavirenz the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing efavirenz is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.