ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of efavirenz.

Excipient: each hard capsule contains 28.5 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

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

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 years of age and older.

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

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

4.2 Posology and method of administration

Posology

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

Concomitant antiretroviral therapy: SUSTIVA must be given in combination with other antiretroviral medicines (see section 4.5).

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

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

Adults: the recommended dose of SUSTIVA 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 SUSTIVA is coadministered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the SUSTIVA 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 SUSTIVA is coadministered with rifampicin, an increase in the dose of SUSTIVA 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 (3 to 17 years)**
The recommended dose of SUSTIVA in combination with a PI and/or NRTIs for patients between 3 and 17 years of age is described in Table 1. SUSTIVA hard capsules must only be administered to children who are able to reliably swallow hard capsules. The safety and efficacy of SUSTIVA in children below the age of 3 years or weighing less than 13 kg have not yet been established (see sections 5.1 and 5.2).

**Alternative method of administration:** for children at least 3 years old and weighing at least 13 kg and adults who cannot reliably swallow hard capsules, SUSTIVA oral solution is the preferred formulation. Administration of the capsule contents with a small amount (1-2 teaspoons) of food may be considered for patients who cannot tolerate the oral solution. In a palatability study in healthy adults of efavirenz mixed with applesauce, grape jelly, yogurt, or infant formula, grape jelly received the highest rating of good overall taste. 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 vertically 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. There are limited safety and tolerability data for administration of the capsule contents in paediatric patients.

**Table 1**

Paediatric dose to be administered once daily*

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to &lt; 15</td>
<td>200</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>250</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>300</td>
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<tr>
<td>25 to &lt; 32.5</td>
<td>350</td>
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<tr>
<td>32.5 to &lt; 40</td>
<td>400</td>
</tr>
<tr>
<td>≥ 40</td>
<td>600</td>
</tr>
</tbody>
</table>

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

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

Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Class C) (see section 5.2).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cисaپride, midazolam, triazolam, пimozide, beпридil, or ergot alkaloids (for example, ergотamine, dihydroergотamine, ergонovine, and methylеrgонovine) because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects [for example, cardiac arrhythmias, prolonged sedation or respiratory depression] (see section 4.5).

Herbal preparations containing St. John’s wort (Hypericum perforatum) must not be used while taking efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

4.4 Special warnings and precautions for use

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance (see section 5.1).

Co-administration of efavirenz with the fixed combination tablet containing efavirenz, emtricitabine, and тenofovir дисoproксил fumarate is not recommended.

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

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

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

Rash: mild-to-moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus (see section 4.8).

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

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

**Nervous system symptoms:** symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

**Seizures:** convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

**Hepatic events:** a few of the 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.

**Effect of food:** the administration of SUSTIVA 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 SUSTIVA 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.

**Lipodystrophy and metabolic abnormalities:** combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

**Osteonecrosis:** although the etiology 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 years of age or who weigh less than 13 kg. Therefore, efavirenz should not be given to children less than 3 years of age.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4 (see section 5.2). Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.

Contraindications of concomitant use

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine,
ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

**St. John’s wort (Hypericum perforatum):** co-administration of efavirenz and St. John’s wort or herbal preparations containing St. John’s wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John’s wort due to induction of drug metabolising enzymes and/or transport proteins by St. John’s wort. If a patient is already taking St. John’s wort, stop St. John’s wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John’s wort and the dose of efavirenz may need adjusting. The inducing effect of St. John’s wort may persist for at least 2 weeks after cessation of treatment. (see section 4.3).

**Other interactions**
Interactions between efavirenz and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in Table 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**

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
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<tr>
<td><strong>Antiretrovirals</strong></td>
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<tr>
<td><strong>Protease inhibitors (PI)</strong></td>
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<tr>
<td>Atazanavir/ritonavir/Efavirenz (400 mg once daily/100 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm): AUC: ↔* ([9 to 10])&lt;sup&gt;a&lt;/sup&gt; C&lt;sub&gt;max&lt;/sub&gt;: ↑17%* ([8 to 27]) C&lt;sub&gt;min&lt;/sub&gt;: ↓42%* ([31 to 51])</td>
<td>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.</td>
</tr>
<tr>
<td>Atazanavir/ritonavir/Efavirenz (400 mg once daily/200 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm): AUC: ↔<em>/** ([10 to 26]) C&lt;sub&gt;max&lt;/sub&gt;: ↔</em>/** ([5 to 26]) C&lt;sub&gt;min&lt;/sub&gt;: ↑12%*/** ([16 to 49]) (CYP3A4 induction). * When compared to atazanavir 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C&lt;sub&gt;min&lt;/sub&gt; might negatively impact the efficacy of atazanavir. ** based on historical comparison</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir/Efavirenz (300 mg twice daily*/100 mg twice daily/600 mg once daily)</td>
<td>Darunavir: AUC: ↓13% C&lt;sub&gt;min&lt;/sub&gt;: ↓31% (CYP3A4 induction) Efavirenz: AUC: ↑21% C&lt;sub&gt;min&lt;/sub&gt;: ↑17% (CYP3A4 inhibition)</td>
<td>The clinical significance of the changes has not been established. Similar findings are expected with the approved darunavir/ritonavir 600/100 mg twice daily dose. This combination should be used with caution. See ritonavir row below.</td>
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<tr>
<td>*lower than recommended dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir/Efavirenz (700 mg twice daily/100 mg twice daily/600 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction</td>
<td>No dose adjustment is necessary for any of these medicinal products. See also ritonavir row below.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels</td>
<td>Recommendation concerning co-administration with efavirenz</td>
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<td>------------------------------------------------</td>
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</tr>
<tr>
<td>Fosamprenavir/Nelfinavir/ Efavirenz</td>
<td>Interaction not studied.</td>
<td>No dose adjustment is necessary for any of these medicinal products. Not recommended as the exposure to both PIs is expected to be significantly decreased.</td>
</tr>
<tr>
<td>Fosamprenavir/Saquinariv/ Efavirenz</td>
<td>Interaction not studied.</td>
<td></td>
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<tr>
<td><strong>Indinavir/Efavirenz (800 mg q8h/200 mg once daily)</strong></td>
<td><strong>Indinavir:</strong>&lt;br&gt;AUC: ↓ 31% (↓ 8 to ↓ 47)&lt;br&gt;C&lt;sub&gt;max&lt;/sub&gt;: ↓ 40%&lt;br&gt;A similar reduction in indinavir exposures was observed when indinavir 1000 mg q8h was given with efavirenz 600 mg daily.&lt;br&gt;(CYP3A4 induction)&lt;br&gt;Efavirenz: No clinically significant pharmacokinetic interaction</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Indinavir/ritonavir/Efavirenz (800 mg twice daily/100 mg twice daily/600 mg once daily)</strong></td>
<td><strong>Indinavir:</strong>&lt;br&gt;AUC: ↓ 25% (↓ 16 to ↓ 32)&lt;br&gt;C&lt;sub&gt;max&lt;/sub&gt;: ↓ 17% (↓ 6 to ↓ 26)&lt;br&gt;C&lt;sub&gt;min&lt;/sub&gt;: ↓ 50% (↓ 40 to ↓ 59)&lt;br&gt;Efavirenz: No clinically significant pharmacokinetic interaction&lt;br&gt;The geometric mean C&lt;sub&gt;min&lt;/sub&gt; for indinavir (0.33 mg/l) when given with ritonavir and efavirenz was higher than the mean historical C&lt;sub&gt;min&lt;/sub&gt; (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.</td>
<td>No dose adjustment is necessary for efavirenz when given with indinavir or indinavir/ritonavir. See also ritonavir row below.</td>
</tr>
<tr>
<td><strong>Lopinavir/ritonavir soft capsules or oral solution/Efavirenz</strong></td>
<td><strong>Substantial decrease in lopinavir exposure.</strong>&lt;br&gt;Lopinavir concentrations: ↓ 30-40%&lt;br&gt;Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Lopinavir/ritonavir tablets/ Efavirenz</strong>&lt;br&gt;(400/100 mg twice daily/600 mg once daily)&lt;br&gt;(500/125 mg twice daily/600 mg once daily)</td>
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<tr>
<td><strong>Nelfinavir/Efavirenz (750 mg q8h/600 mg once daily)</strong></td>
<td><strong>Nelfinavir:</strong>&lt;br&gt;AUC: ↑ 20% (↑ 8 to ↑ 34)&lt;br&gt;C&lt;sub&gt;max&lt;/sub&gt;: ↑ 21% (↑ 10 to ↑ 33)&lt;br&gt;The combination was generally well tolerated.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
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<td>---------------------------------------------</td>
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<tr>
<td>Ritonavir/Efavirenz (500 mg twice daily/600 mg once daily)</td>
<td>Ritonavir: Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔ Morning C&lt;sub&gt;max&lt;/sub&gt;: ↑ 24% (↑ 12 to ↑ 38) Evening C&lt;sub&gt;max&lt;/sub&gt;: ↔ Morning C&lt;sub&gt;min&lt;/sub&gt;: ↑ 42% (↑ 9 to ↑ 86) &lt;sup&gt;b&lt;/sup&gt; Evening C&lt;sub&gt;min&lt;/sub&gt;: ↑ 24% (↑ 3 to ↑ 50) &lt;sup&gt;b&lt;/sup&gt; Efavirenz: AUC: ↑ 21% (↑ 10 to ↑ 34) C&lt;sub&gt;max&lt;/sub&gt;: ↑ 14% (↑ 4 to ↑ 26) C&lt;sub&gt;min&lt;/sub&gt;: ↑ 25% (↑ 7 to ↑ 46) &lt;sup&gt;b&lt;/sup&gt; (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.</td>
<td>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.</td>
</tr>
<tr>
<td>Saquinavir/ritonavir/Efavirenz</td>
<td>Interaction not studied.</td>
<td>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.</td>
</tr>
<tr>
<td>CCR5 antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc/Efavirenz (100 mg twice daily/600 mg once daily)</td>
<td>Maraviroc: AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 45% (↓ 38 to ↓ 51) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 51% (↓ 37 to ↓ 62) Efavirenz concentrations not measured, no effect is expected.</td>
<td>Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc.</td>
</tr>
<tr>
<td>Integrase strand transfer inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir/Efavirenz (400 mg single dose/ -)</td>
<td>Raltegravir: AUC: ↓ 36% C&lt;sub&gt;12&lt;/sub&gt;: ↓ 21% C&lt;sub&gt;max&lt;/sub&gt;: ↓ 36% (UGT1A1 induction)</td>
<td>No dose adjustment is necessary for raltegravir.</td>
</tr>
<tr>
<td>NRTIs and NNRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTIs/Efavirenz</td>
<td>Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine, and tenofovir disoproxil fumarate. Clinically significant interactions are not expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>NNRTIs/Efavirenz</td>
<td>Interaction not studied.</td>
<td>Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of efavirenz</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td>and another NNRTI is not recommended.</td>
</tr>
<tr>
<td>Azithromycin/Efavirenz (600 mg single dose/400 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>Clarithromycin/Efavirenz (500 mg q12h/400 mg once daily)</td>
<td>Clarithromycin: AUC: ↓ 39% (↓ 30 to ↓ 46) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 26% (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34% (↑ 18 to ↑ 53) C&lt;sub&gt;max&lt;/sub&gt;: ↑ 49% (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ C&lt;sub&gt;max&lt;/sub&gt;: ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin.</td>
<td>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.</td>
</tr>
<tr>
<td>Other macrolide antibiotics (e.g.,erythromycin)/Efavirenz</td>
<td>Interaction not studied.</td>
<td>No data are available to make a dose recommendation.</td>
</tr>
<tr>
<td><strong>Antimycobacterials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin/Efavirenz (300 mg once daily/600 mg once daily)</td>
<td>Rifabutin: AUC: ↓ 38% (↓ 28 to ↓ 47) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 32% (↓ 15 to ↓ 46) C&lt;sub&gt;min&lt;/sub&gt;: ↓ 45% (↓ 31 to ↓ 56) Efavirenz: AUC: ↔ C&lt;sub&gt;max&lt;/sub&gt;: ↔ C&lt;sub&gt;min&lt;/sub&gt;: ↓ 12% (↓ 24 to ↑ 1) (CYP3A4 induction)</td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin/Efavirenz (600 mg once daily/600 mg once daily)</td>
<td>Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 20% (↓ 11 to ↓ 28) C&lt;sub&gt;min&lt;/sub&gt;: ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)</td>
<td>When taken with rifampicin, 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.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C\text{max}, C\text{min} with confidence intervals if available(^a) (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole/Efavirenz (200 mg q12h/600 mg once daily)</td>
<td>Itraconazole: AUC: ↓ 39% (↓ 21 to ↓ 53) C\text{max}: ↓ 37% (↓ 20 to ↓ 51) C\text{min}: ↓ 44% (↓ 27 to ↓ 58) (decrease in itraconazole concentrations: CYP3A4 induction) Hydroxyitraconazole: AUC: ↓ 37% (↓ 14 to ↓ 55) C\text{max}: ↓ 35% (↓ 12 to ↓ 52) C\text{min}: ↓ 43% (↓ 18 to ↓ 60) Efavirenz: No clinically significant pharmacokinetic change.</td>
<td>Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.</td>
</tr>
<tr>
<td>Posaconazole/Efavirenz --/400 mg once daily</td>
<td>Posaconazole: AUC: ↓ 50% C\text{max}: ↓ 45% (UDP-G induction)</td>
<td>Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.</td>
</tr>
<tr>
<td>Voriconazole/Efavirenz (200 mg twice daily/400 mg once daily)</td>
<td>Voriconazole: AUC: ↓ 77% C\text{max}: ↓ 61% Efavirenz: AUC: ↑ 44% C\text{max}: ↑ 38% Voriconazole: AUC: ↓ 7% (↓ 23 to ↑ 13) * C\text{max}: ↑ 23% (↓ 1 to ↑ 53) * Efavirenz: AUC: ↑ 17% (↑ 6 to ↑ 29) ** C\text{max}: ↔ ** *compared to 200 mg twice daily alone **compared to 600 mg once daily alone (competitive inhibition of oxidative metabolism)</td>
<td>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.</td>
</tr>
<tr>
<td>Voriconazole/Efavirenz (400 mg twice daily/300 mg once daily)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole/Efavirenz (200 mg once daily/400 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>Ketoconazole and other imidazole antifungals</td>
<td>Interaction not studied</td>
<td>No data are available to make a dose recommendation.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td><strong>ACID REDUCING AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminium hydroxide-magnesium hydroxide-simethicone antacid/Efavirenz (30 ml single dose/400 mg single dose)</td>
<td>Neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz.</td>
<td>Co-administration of efavirenz with medicinal products that alter gastric pH would not be expected to affect efavirenz absorption.</td>
</tr>
<tr>
<td>Famotidine/Efavirenz (40 mg single dose/400 mg single dose)</td>
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<td></td>
</tr>
<tr>
<td><strong>ANTIANXIETY AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam/Efavirenz (2 mg single dose/600 mg once daily)</td>
<td>Lorazepam: AUC: ↑ 7% (↑ 1 to ↑ 14) C&lt;sub&gt;max&lt;/sub&gt;: ↑ 16% (↑ 2 to ↑ 32) These changes are not considered clinically significant.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin/Efavirenz</td>
<td>Interaction not studied. Plasma concentrations and effects of warfarin are potentially increased or decreased by efavirenz.</td>
<td>Dose adjustment of warfarin may be required.</td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Carbamazepine/Efavirenz (400 mg once daily/600 mg once daily) | Carbamazepine: AUC: ↓ 27% (↓ 20 to ↓ 33) C<sub>max</sub>: ↓ 20% (↓ 15 to ↓ 24)  
C<sub>min</sub>: ↓ 35% (↓ 24 to ↓ 44)  
Efavirenz: AUC: ↓ 36% (↓ 32 to ↓ 40)  
C<sub>max</sub>: ↓ 21% (↓ 15 to ↓ 26)  
C<sub>min</sub>: ↓ 47% (↓ 41 to ↓ 53) (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction)  
The steady-state AUC, C<sub>max</sub> and C<sub>min</sub> 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. |
<p>| 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. |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigabatrin/Efavirenz Gabapentin/Efavirenz</td>
<td>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.</td>
<td>No dose adjustment is necessary for any of these medicinal products.</td>
</tr>
</tbody>
</table>

**ANTIDEPRESSANTS**

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

| Sertraline/Efavirenz (50 mg once daily/600 mg once daily) | Sertraline:  
AUC: ↓ 39% (↓ 27 to ↓ 50)  
C<sub>max</sub>: ↓ 29% (↓ 15 to ↓ 40)  
C<sub>min</sub>: ↓ 46% (↓ 31 to ↓ 58)  
Efavirenz:  
AUC: ↔   
C<sub>max</sub>: ↑ 11% (↑ 6 to ↑ 16)  
C<sub>min</sub>: ↔ (CYP3A4 induction) | Sertraline dose increases should be guided by clinical response. No dose adjustment is necessary for efavirenz. |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine/Efavirenz (20 mg once daily/600 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>Fluoxetine/Efavirenz</td>
<td>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.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
</tbody>
</table>

**ANTIHISTAMINES**

| Cetirizine/Efavirenz (10 mg single dose/600 mg once daily) | Cetirizine:  
AUC: ↔   
C<sub>max</sub>: ↓ 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. |
### CARDIOVASCULAR AGENTS

#### Calcium Channel Blockers

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| **Diltiazem/Efavirenz** (240 mg once daily/600 mg once daily) | Diltiazem:  
AUC: ↓ 69% (↓ 55 to ↓ 79)  
C<sub>max</sub>: ↓ 60% (↓ 50 to ↓ 68)  
C<sub>min</sub>: ↓ 63% (↓ 44 to ↓ 75)  
Desacetyl diltiazem:  
AUC: ↓ 75% (↓ 59 to ↓ 84)  
C<sub>max</sub>: ↓ 64% (↓ 57 to ↓ 69)  
C<sub>min</sub>: ↓ 62% (↓ 44 to ↓ 75)  
N-monodesmethyl diltiazem:  
AUC: ↓ 75% (↓ 59 to ↓ 84)  
C<sub>max</sub>: ↓ 64% (↓ 57 to ↓ 69)  
C<sub>min</sub>: ↓ 62% (↓ 44 to ↓ 75)  
Efavirenz:  
AUC: ↑ 11% (↑ 5 to ↑ 18)  
C<sub>max</sub>: ↑ 16% (↑ 6 to ↑ 26)  
C<sub>min</sub>: ↑ 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

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| **Atorvastatin/Efavirenz** (10 mg once daily/600 mg once daily) | Atorvastatin:  
AUC: ↓ 43% (↓ 34 to ↓ 50)  
C<sub>max</sub>: ↓ 12% (↓ 1 to ↓ 26)  
2-hydroxy atorvastatin:  
AUC: ↓ 35% (↓ 13 to ↓ 40)  
C<sub>max</sub>: ↓ 13% (↓ 0 to ↓ 23)  
4-hydroxy atorvastatin:  
AUC: ↓ 4% (↓ 0 to ↓ 31)  
C<sub>max</sub>: ↓ 47% (↓ 9 to ↓ 51)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 34% (↓ 21 to ↓ 41)  
C<sub>max</sub>: ↓ 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<sub>max</sub>: ↓ 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available (^a) (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| 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 | Interaction not studied. 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). |
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:  
\( AUC: \downarrow 52\% (\downarrow 33 \text{ to } \downarrow 66) \)  
\( C_{\text{max}}: \downarrow 45\% (\downarrow 25 \text{ to } \downarrow 59) \)  
(CYP3A4 induction)  
In a study of HIV infected intravenous drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms.  
Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Buprenorphine/naloxone/Efavirenz  
Buprenorphine:  
\( AUC: \downarrow 50\% \)  
Norbuprenorphine:  
\( AUC: \downarrow 71\% \)  
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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Efavirenz should not be used during pregnancy unless there are no other appropriate treatment options.

Women of childbearing potential: pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.

Pregnancy: there are limited amount of data from the use of efavirenz in pregnant women. In postmarketing experience through an antiretroviral pregnancy registry, outcomes for more than 400 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been prospectively reported with no specific malformation pattern observed. A small number of cases of neural tube defects, including meningomyelocele, have been reported via the registry. Most neural tube defects were isolated retrospectively reported cases, and causality cannot be
ruled out but has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects (see section 5.3).

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

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

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

*a. Summary of the safety profile*

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported adverse reactions of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most notable adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2 - 4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; psychiatric adverse reactions including severe depression, death by suicide, and psychosis like behaviour; and seizures have been reported in patients treated with efavirenz. The administration of SUSTIVA with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

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

*b. Tabulated list of adverse reactions*

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below. Also listed in italics are adverse reactions observed post-marketing in association with efavirenz-containing antiretroviral treatment regimens. Frequency is defined using the following convention: very common (≥ 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).

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
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<tr>
<td>---------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>common</td>
<td>abnormal dreams, anxiety, depression,</td>
</tr>
<tr>
<td></td>
<td>insomnia*</td>
</tr>
<tr>
<td>uncommon</td>
<td>affect lability, aggression, confusional</td>
</tr>
<tr>
<td></td>
<td>state, euphoric mood, hallucination, mania,</td>
</tr>
<tr>
<td></td>
<td>paranoia, psychosis†, suicide attempt,</td>
</tr>
<tr>
<td></td>
<td>suicide ideation*</td>
</tr>
<tr>
<td>rare</td>
<td>delusion†, neurosis†, completed suicide†*</td>
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<td></td>
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<tr>
<td>Nervous system disorders</td>
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</tr>
<tr>
<td>common</td>
<td>cerebellar coordination and balance</td>
</tr>
<tr>
<td></td>
<td>disturbances†, disturbance in attention</td>
</tr>
<tr>
<td></td>
<td>(3.6%), dizziness (8.5%), headache (5.7%),</td>
</tr>
<tr>
<td></td>
<td>somnolence (2.0%)*</td>
</tr>
<tr>
<td>uncommon</td>
<td>agitation, amnesia, ataxia, coordination</td>
</tr>
<tr>
<td></td>
<td>abnormal, convulsions, thinking abnormal,*</td>
</tr>
<tr>
<td></td>
<td>tremor†</td>
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<td></td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>vision blurred</td>
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<td></td>
<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>tinnitus†, vertigo</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>flushing†</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>common</td>
<td>abdominal pain, diarrhoea, nausea, vomiting</td>
</tr>
<tr>
<td>uncommon</td>
<td>pancreatitis</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>hepatitis acute</td>
</tr>
<tr>
<td>rare</td>
<td>hepatic failure†*</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>very common</td>
<td>rash (11.6%)*</td>
</tr>
<tr>
<td>common</td>
<td>pruritus</td>
</tr>
<tr>
<td>uncommon</td>
<td>erythema multiforme, Stevens-Johnson</td>
</tr>
<tr>
<td></td>
<td>syndrome*</td>
</tr>
<tr>
<td>rare</td>
<td>photoallergic dermatitis†</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast</td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>gynaecomastia</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration</td>
<td></td>
</tr>
<tr>
<td>site conditions</td>
<td></td>
</tr>
<tr>
<td>common</td>
<td>fatigue</td>
</tr>
</tbody>
</table>

*See section c. Description of selected adverse reactions for more details.
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).

c. Description of selected adverse reactions

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:

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz regimen (n=1,008)</th>
<th>Control regimen (n=635)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- severe depression</td>
<td>1.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>- suicidal ideation</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- non-fatal suicide attempts</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>- aggressive behaviour</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- paranoid reactions</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- manic reactions</td>
<td>0.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

Nervous system symptoms: in clinical controlled trials, frequently reported adverse reactions included, but were not limited to dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms of moderate-to-severe intensity were experienced by 19% (severe 2%) of patients compared to 9% (severe 1%) of patients receiving control regimens. In clinical studies 2% of patients treated with efavirenz discontinued therapy due to such symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Nervous system symptoms may occur more frequently when efavirenz is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms and can be recommended during the first weeks of therapy.
and in patients who continue to experience these symptoms (see section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit.

Analysis of long-term data showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the control arm.

**Hepatic failure:** A few of the 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 (see section 4.4).

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

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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

**Laboratory test abnormalities:**

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

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

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

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

d. Paediatric population

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

e. Other special populations

Liver enzymes in hepatitis B or C co-infected patients: in the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these 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 liver disorders (see section 4.4).

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: 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).

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 medications used in combination with efavirenz.

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

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

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

Clinical efficacy:

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

Two controlled studies (006 and ACTG 364) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naïve and NRTI-experienced HIV-infected patients. Study 020 showed similar activity in NRTI-experienced patients over 24 weeks. In these studies the dose of efavirenz was 600 mg once daily; the dose of indinavir was 1,000 mg every 8 hours when used with efavirenz and 800 mg every 8 hours when used without efavirenz. The dose of nelfinavir was 750 mg given three times a day. The standard doses of NRTIs given every 12 hours were used in each of these studies.

Study 006, a randomized, open-label trial, compared efavirenz + zidovudine + lamivudine or efavirenz + indinavir with indinavir + zidovudine + lamivudine in 1,266 patients who were required to be efavirenz-, lamivudine-, NNRTI-, and PI-naïve at study entry. The mean baseline CD4 cell count was 341 cells/mm³ and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 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

| Treatment Regimen \n|------------------|------------------|------------------|------------------|
|                  | n               | 48 weeks        | 48 weeks        | 48 weeks        |
| EFV + ZDV + 3TC  | 202             | 67% (60%, 73%)  | 62% (55%, 69%)  | 187             |
| EFV + IDV        | 206             | 54% (47%, 61%)  | 48% (41%, 55%)  | 177             |
| IDV + ZDV + 3TC  | 206             | 45% (38%, 52%)  | 40% (34%, 47%)  | 153             |

\[a\] 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

| Study Number/ Treatment Regimens \n|------------------|------------------|------------------|
|                  | n               | % (95% C.I.\(^b\)) | % (95% C.I.\(^b\)) | Mean change from baseline-CD4 cell count |
| Study ACTG 364 \n48 weeks | < 500 copies/ml | < 50 copies/ml | cells/mm\(^d\) | (S.E.M.\(^d\)) |
| 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 \n24 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.  
\[b\] C.I., confidence interval for proportion of patients in response.  
\[c\] S.E.M., standard error of the mean.  
\[d\] EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir.

---, not performed.
**Paediatric population:** ACTG 382 is an ongoing uncontrolled study of 57 NRTI-experienced paediatric patients (3 - 16 years) which characterises the pharmacokinetics, antiviral activity and safety of efavirenz in combination with nelfinavir (20 - 30 mg/kg given three times a day) and one or more NRTIs. The starting dose of efavirenz was the equivalent of a 600 mg dose (adjusted from calculated body size based on weight). The response rate, based on the NC = F analysis of the percentage of patients with plasma HIV-RNA < 400 copies/ml at 48 weeks was 60% (95%, C.I. 47, 72), and 53% (C.I. 40, 66) based on percentage of patients with plasma HIV-RNA < 50 copies/ml. The mean CD4 cell counts were increased by 63 ± 34.5 cells/mm³ from baseline. The durability of the response was similar to that seen in adult patients.

### 5.2 Pharmacokinetic properties

**Absorption:** peak efavirenz plasma concentrations of 1.6 - 9.1 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<sub>max</sub> 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<sub>max</sub>, mean C<sub>min</sub>, 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<sub>max</sub> was 12.9 ± 3.7 μM (29%) [mean ± S.D. (% C.V.)], steady state C<sub>min</sub> 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 P450 enzymes, resulting in the induction of its own metabolism. 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).

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

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

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

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

5.3 Preclinical safety data
Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays.

Efavirenz induced foetal resorptions in rats. Malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, microphthalmia 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

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)  

6.2 Incompatibilities  

Not applicable.  

6.3 Shelf life  

3 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 hard capsules.  

6.6 Special precautions for disposal  

No special requirements.  

7. MARKETING AUTHORISATION HOLDER  

Bristol-Myers Squibb Pharma EEIG  
Uxbridge Business Park, Sanderson Road  
Uxbridge UB8 1DH  
United Kingdom  

8. MARKETING AUTHORISATION NUMBER(S)  

EU/1/99/110/001 - bottle  

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION  

Date of first authorisation: 28 May 1999  
Date of latest renewal: 28 May 2009
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 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains 100 mg of efavirenz.
Excipient: each hard capsule contains 57.0 mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard capsule
White, printed with "SUSTIVA" on the body and "100 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 years of age and older.
SUSTIVA has not been adequately studied in patients with advanced HIV disease, namely in patients with CD4 counts < 50 cells/mm³, or after failure of protease inhibitor (PI) containing regimens. Although cross-resistance of efavirenz with PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based combination therapy after failure of regimens containing SUSTIVA.
For a summary of clinical and pharmacodynamic information, see section 5.1.

4.2 Posology and method of administration

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

Concomitant antiretroviral therapy: SUSTIVA must be given in combination with other antiretroviral medicines (see section 4.5).

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

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

Adults: the recommended dose of SUSTIVA 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 SUSTIVA is coadministered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the SUSTIVA 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 SUSTIVA is coadministered with rifampicin, an increase in the dose of SUSTIVA 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 (3 to 17 years)**
The recommended dose of SUSTIVA in combination with a PI and/or NRTIs for patients between 3 and 17 years of age is described in Table 1. SUSTIVA hard capsules must only be administered to children who are able to reliably swallow hard capsules. The safety and efficacy of SUSTIVA in children below the age of 3 years or weighing less than 13 kg have not yet been established (see sections 5.1 and 5.2).

**Alternative method of administration:** for children at least 3 years old and weighing at least 13 kg and adults who cannot reliably swallow hard capsules, SUSTIVA oral solution is the preferred formulation. Administration of the capsule contents with a small amount (1-2 teaspoons) of food may be considered for patients who cannot tolerate the oral solution. In a palatability study in healthy adults of efavirenz mixed with applesauce, grape jelly, yogurt, or infant formula, grape jelly received the highest rating of good overall taste. 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 vertically 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. There are limited safety and tolerability data for administration of the capsule contents in paediatric patients.

**Table 1**
**Paediatric dose to be administered once daily***

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to &lt; 15</td>
<td>200</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>250</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>300</td>
</tr>
<tr>
<td>25 to &lt; 32.5</td>
<td>350</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>400</td>
</tr>
<tr>
<td>≥ 40</td>
<td>600</td>
</tr>
</tbody>
</table>

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

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.
Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Class C) (see section 5.2).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects [for example, cardiac arrhythmias, prolonged sedation or respiratory depression] (see section 4.5).

Herbal preparations containing St. John’s wort (Hypericum perforatum) must not be used while taking efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

4.4 Special warnings and precautions for use

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance (see section 5.1).

Co-administration of efavirenz with the fixed combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate is not recommended.

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

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

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

**Rash:** mild-to-moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus (see section 4.8).

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

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

Nervous system symptoms: symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Seizures: convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

Hepatic events: a few of the 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.

Effect of food: the administration of SUSTIVA 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 SUSTIVA 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.

Lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Osteonecrosis: although the etiology 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 years of age or who weigh less than 13 kg. Therefore, efavirenz should not be given to children less than 3 years of age.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4 (see section 5.2). Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.

Contraindications of concomitant use
Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozone, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

St. John’s wort (Hypericum perforatum): co-administration of efavirenz and St. John’s wort or herbal preparations containing St. John’s wort is contraindicated. Plasma levels of efavirenz can be reduced
by concomitant use of St. John’s wort due to induction of drug metabolising enzymes and/or transport proteins by St. John’s wort. If a patient is already taking St. John’s wort, stop St. John’s wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John’s wort and the dose of efavirenz may need adjusting. The inducing effect of St. John’s wort may persist for at least 2 weeks after cessation of treatment. (see section 4.3).

Other interactions
Interactions between efavirenz and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in Table 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

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C\text{max}, C\text{min} with confidence intervals if available(^a) (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors (PI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/ritonavir/Efavirenz (400 mg once daily/100 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm): AUC: ↔* (9 to 110) C\text{max}: ↑17%* (8 to 27) C\text{min}: ↓42%* (13 to 51) (CYP3A4 induction).</td>
<td>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.</td>
</tr>
<tr>
<td>Atazanavir/ritonavir/Efavirenz (400 mg once daily/200 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm): AUC: ↔<em>/** (8 to 26) C\text{max}: ↔</em>/** (5 to 26) C\text{min}: ↑12%*/** (16 to 49) (CYP3A4 induction). * When compared to atazanavir 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C\text{min} might negatively impact the efficacy of atazanavir. ** Based on historical comparison.</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir/Efavirenz (300 mg twice daily*/100 mg twice daily/600 mg once daily)</td>
<td>Darunavir: AUC: ↓13% C\text{min}: ↓31% (CYP3A4 induction) Efavirenz: AUC: ↑21% C\text{min}: ↑17% (CYP3A4 inhibition)</td>
<td>The clinical significance of the changes has not been established. Similar findings are expected with the approved darunavir/ritonavir 600/100 mg twice daily dose. This combination should be used with caution. See ritonavir row below.</td>
</tr>
<tr>
<td>*lower than recommended dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir/Efavirenz (700 mg twice daily/100 mg twice daily/600 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction</td>
<td>No dose adjustment is necessary for any of these medicinal products. See also ritonavir row below.</td>
</tr>
<tr>
<td>Fosamprenavir/Nelfinavir/ Efavirenz</td>
<td>Interaction not studied.</td>
<td>No dose adjustment is necessary for any of these medicinal products. Not recommended as the exposure to both PIs is expected to be significantly decreased.</td>
</tr>
<tr>
<td>Fosamprenavir/Saquinavir/ Efavirenz</td>
<td>Interaction not studied.</td>
<td></td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Indinavir/Efavirenz (800 mg q8h/200 mg once daily) | **Indinavir:**  
AUC: ↓ 31% (↓ 8 to ↓ 47)  
C<sub>min</sub>: ↓ 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)<sup>b</sup>  
C<sub>max</sub>: ↓ 17% (↓ 6 to ↓ 26)<sup>b</sup>  
C<sub>min</sub>: ↓ 50% (↓ 40 to ↓ 59)<sup>b</sup>  
**Efavirenz:** No clinically significant pharmacokinetic interaction  
The geometric mean C<sub>min</sub> for indinavir (0.33 mg/l) when given with ritonavir and efavirenz was higher than the mean historical C<sub>min</sub> (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. |
| 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<sub>max</sub>: ↑ 21% (↑ 10 to ↑ 33)  
The combination was generally well tolerated. | No dose adjustment is necessary for either medicinal product. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, $C_{\text{max}}$, $C_{\text{min}}$ with confidence intervals if available (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ritonavir/Efavirenz</strong>&lt;br&gt;(500 mg twice daily/600 mg once daily)</td>
<td><strong>Ritonavir:</strong>&lt;br&gt;Morning AUC: ↑ 18% ($\uparrow$ 6 to $\uparrow$ 33)&lt;br&gt;Evening AUC: ↔&lt;br&gt;Morning $C_{\text{max}}$: ↑ 24% ($\uparrow$ 12 to $\uparrow$ 38)&lt;br&gt;Evening $C_{\text{max}}$: ↔&lt;br&gt;Morning $C_{\text{min}}$: ↑ 42% ($\uparrow$ 9 to $\uparrow$ 86)&lt;br&gt;Evening $C_{\text{min}}$: ↑ 24% ($\uparrow$ 3 to $\uparrow$ 50)&lt;br&gt;&lt;br&gt;<strong>Efavirenz:</strong>&lt;br&gt;AUC: ↑ 21% ($\uparrow$ 10 to $\uparrow$ 34)&lt;br&gt;$C_{\text{max}}$: ↑ 14% ($\uparrow$ 4 to $\uparrow$ 26)&lt;br&gt;$C_{\text{min}}$: ↑ 25% ($\uparrow$ 7 to $\uparrow$ 46)&lt;br&gt;(inhibition of CYP-mediated oxidative metabolism)&lt;br&gt;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.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Saquinavir/ritonavir/Efavirenz</strong></td>
<td>Interaction not studied.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>CCR5 antagonist</strong></td>
<td><strong>Maraviroc/Efavirenz</strong>&lt;br&gt;(100 mg twice daily/600 mg once daily)</td>
<td><strong>Maraviroc:</strong>&lt;br&gt;AUC: ↓ 45% ($\downarrow$ 38 to $\downarrow$ 51)&lt;br&gt;$C_{\text{max}}$: ↓ 51% ($\downarrow$ 37 to $\downarrow$ 62)&lt;br&gt;Efavirenz concentrations not measured, no effect is expected.</td>
</tr>
<tr>
<td><strong>Integrase strand transfer inhibitor</strong></td>
<td><strong>Raltegravir/Efavirenz</strong>&lt;br&gt;(400 mg single dose/ -)</td>
<td><strong>Raltegravir:</strong>&lt;br&gt;AUC: ↓ 36%&lt;br&gt;$C_{\text{12}}$: ↓ 21%&lt;br&gt;$C_{\text{max}}$: ↓ 36%&lt;br&gt;(UGT1A1 induction)&lt;br&gt;No dose adjustment is necessary for raltegravir.</td>
</tr>
<tr>
<td><strong>NRTIs and NNRTIs</strong></td>
<td><strong>NRTIs/Efavirenz</strong></td>
<td>Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine, and tenofovir disoproxil fumarate. Clinically significant interactions are not expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.</td>
</tr>
<tr>
<td></td>
<td><strong>NNRTIs/Efavirenz</strong></td>
<td>Interaction not studied.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td>and another NNRTI is not recommended.</td>
</tr>
<tr>
<td>Azithromycin/Efavirenz (600 mg single dose/400 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
</tbody>
</table>
| Clarithromycin/Efavirenz (500 mg q12h/400 mg once daily) | Clarithromycin:  
AUC: ↓ 39% (↓ 30 to ↓ 46)  
C<sub>max</sub>: ↓ 26% (↓ 15 to ↓ 35)  
Clarithromycin 14-hydroxymetabolite:  
AUC: ↑ 34% (↑ 18 to ↑ 53)  
C<sub>max</sub>: ↑ 49% (↑ 32 to ↑ 69)  
Efavirenz:  
AUC: ↔  
C<sub>max</sub>: ↑ 11% (↑ 3 to ↑ 19)  
(CYP3A4 induction)  
Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin. | The clinical significance of these changes in clarithromycin plasma levels is not known.  
Alternatives to clarithromycin (e.g. azithromycin) may be considered. No dose adjustment is necessary for efavirenz. |
| Other macrolide antibiotics (e.g., erythromycin)/Efavirenz | Interaction not studied.                                                                                       | No data are available to make a dose recommendation.        |
| **Antimycobacterials**                         |                                                                                                                 |                                                             |
| Rifabutin/Efavirenz (300 mg once daily/600 mg once daily) | Rifabutin:  
AUC: ↓ 38% (↓ 28 to ↓ 47)  
C<sub>max</sub>: ↓ 32% (↓ 15 to ↓ 46)  
C<sub>min</sub>: ↓ 45% (↓ 31 to ↓ 56)  
Efavirenz:  
AUC: ↔  
C<sub>max</sub>: ↔  
C<sub>min</sub>: ↓ 12% (↓ 24 to ↑ 1)  
(CYP3A4 induction)  
Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin. | 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). No dose adjustment is necessary for rifampicin. |
| Rifampicin/Efavirenz (600 mg once daily/600 mg once daily) | Efavirenz:  
AUC: ↓ 26% (↓ 15 to ↓ 36)  
C<sub>max</sub>: ↓ 20% (↓ 11 to ↓ 28)  
C<sub>min</sub>: ↓ 32% (↓ 15 to ↓ 46)  
(CYP3A4 and CYP2B6 induction)  
Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin. | When taken with rifampicin, 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, $C_{\text{max}}$, $C_{\text{min}}$ with confidence intervals if available$^a$ (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Itraconazole/Efavirenz (200 mg q12h/600 mg once daily) | Itraconazole:  
AUC: ↓ 39% (↓ 21 to ↓ 53)  
$C_{\text{max}}$: ↓ 37% (↓ 20 to ↓ 51)  
$C_{\text{min}}$: ↓ 44% (↓ 27 to ↓ 58)  
(decrease in itraconazole concentrations: CYP3A4 induction)  
Hydroxyitraconazole:  
AUC: ↓ 37% (↓ 14 to ↓ 55)  
$C_{\text{max}}$: ↓ 35% (↓ 12 to ↓ 52)  
$C_{\text{min}}$: ↓ 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. |
| Posaconazole/Efavirenz -/400 mg once daily | Posaconazole:  
AUC: ↓ 50%  
$C_{\text{max}}$: ↓ 45%  
(UDP-G induction) | Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk. |
| Voriconazole/Efavirenz (200 mg twice daily/400 mg once daily) | Voriconazole:  
AUC: ↓ 77%  
$C_{\text{max}}$: ↓ 61%  
Efavirenz:  
AUC: ↑ 44%  
$C_{\text{max}}$: ↑ 38%  
Voriconazole:  
AUC: ↓ 7% (↓ 23 to ↑ 13) *  
$C_{\text{max}}$: ↑ 23% (↓ 1 to ↑ 53) *  
Efavirenz:  
AUC: ↑ 17% (↑ 6 to ↑ 29) **  
$C_{\text{max}}$: ↔ **  
*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. |
### Medicinal product by therapeutic areas (dose)

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACID REDUCING AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminium hydroxide-magnesium hydroxide-simethicone antacid/Efavirenz (30 ml single dose/400 mg single dose)</td>
<td>Neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz.</td>
<td>Co-administration of efavirenz with medicinal products that alter gastric pH would not be expected to affect efavirenz absorption.</td>
</tr>
<tr>
<td>Famotidine/Efavirenz (40 mg single dose/400 mg single dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTIANGSTY AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam/Efavirenz (2 mg single dose/600 mg once daily)</td>
<td>Lorazepam: AUC: ↑ 7% (↑ 1 to ↑ 14) C&lt;sub&gt;max&lt;/sub&gt;: ↑ 16% (↑ 2 to ↑ 32) These changes are not considered clinically significant.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td>Interaction not studied. Plasma concentrations and effects of warfarin are potentially increased or decreased by efavirenz.</td>
<td>Dose adjustment of warfarin may be required.</td>
</tr>
<tr>
<td>WARFARIN/Efavirenz</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine/Efavirenz (400 mg once daily/600 mg once daily)</td>
<td>Carbamazepine: AUC: ↓ 27% (↓ 20 to ↓ 33) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 20% (↓ 15 to ↓ 24) C&lt;sub&gt;min&lt;/sub&gt;: ↓ 35% (↓ 24 to ↓ 44) Efavirenz: AUC: ↓ 36% (↓ 32 to ↓ 40) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 21% (↓ 15 to ↓ 26) C&lt;sub&gt;min&lt;/sub&gt;: ↓ 47% (↓ 41 to ↓ 53) (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction) The steady-state AUC, C&lt;sub&gt;max&lt;/sub&gt; and C&lt;sub&gt;min&lt;/sub&gt; of the active carbamazepine epoxide metabolite remained unchanged. Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.</td>
<td>No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.</td>
</tr>
<tr>
<td>Phenytoin, Phenobarbital, and other anticonvulsants that are substrates of CYP450 isoenzymes</td>
<td>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.</td>
<td>When efavirenz is co-administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic monitoring of anticonvulsant levels should be conducted.</td>
</tr>
<tr>
<td>Valproic acid/Efavirenz (250 mg twice daily/600 mg once daily)</td>
<td>No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.</td>
<td>No dose adjustment is necessary for efavirenz. Patients should be monitored for seizure control.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, $C_{\text{max}}$, $C_{\text{min}}$ with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Vigabatrin/Efavirenz Gabapentin/Efavirenz</td>
<td>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.</td>
<td>No dose adjustment is necessary for any of these medicinal products.</td>
</tr>
</tbody>
</table>

**ANTIDEPRESSANTS**

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

| Sertraline/Efavirenz (50 mg once daily/600 mg once daily) | Sertraline:  
AUC: ↓ 39% (↓ 27 to ↓ 50)  
$C_{\text{max}}$: ↓ 29% (↓ 15 to ↓ 40)  
$C_{\text{min}}$: ↓ 46% (↓ 31 to ↓ 58)  
Efavirenz:  
AUC: ↔  
$C_{\text{max}}$: ↑ 11% (↑ 6 to ↑ 16)  
$C_{\text{min}}$: ↔ (CYP3A4 induction) | Sertraline dose increases should be guided by clinical response. No dose adjustment is necessary for efavirenz. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine/Efavirenz (20 mg once daily/600 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>Fluoxetine/Efavirenz</td>
<td>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.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
</tbody>
</table>

**ANTIHISTAMINES**

| Cetirizine/Efavirenz (10 mg single dose/600 mg once daily) | Cetirizine:  
AUC: ↔  
$C_{\text{max}}$: ↓ 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| **CARDIOVASCULAR AGENTS**                   | Diltiazem:  
AUC: ↓ 69% (↓ 55 to ↓ 79)  
C<sub>max</sub>: ↓ 60% (↓ 50 to ↓ 68)  
C<sub>min</sub>: ↓ 63% (↓ 44 to ↓ 75)  
Desacetyl diltiazem:  
AUC: ↓ 75% (↓ 59 to ↓ 84)  
C<sub>max</sub>: ↓ 64% (↓ 57 to ↓ 69)  
C<sub>min</sub>: ↓ 62% (↓ 44 to ↓ 75)  
N-monodesmethyl diltiazem:  
AUC: ↓ 37% (↓ 17 to ↓ 52)  
C<sub>max</sub>: ↓ 28% (↓ 7 to ↓ 44)  
C<sub>min</sub>: ↓ 37% (↓ 17 to ↓ 52)  
Efavirenz:  
AUC: ↑ 11% (↑ 5 to ↑ 18)  
C<sub>max</sub>: ↑ 16% (↑ 6 to ↑ 26)  
C<sub>min</sub>: ↑ 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). |

<table>
<thead>
<tr>
<th>LIPID LOWERING MEDICINAL PRODUCTS</th>
<th>HMG Co-A Reductase Inhibitors</th>
<th></th>
</tr>
</thead>
</table>
| Atorvastatin/Efavirenz (10 mg once daily/600 mg once daily) | Atorvastatin:  
AUC: ↓ 43% (↓ 34 to ↓ 50)  
C<sub>max</sub>: ↓ 12% (↓ 1 to ↓ 26)  
2-hydroxy atorvastatin:  
AUC: ↓ 35% (↓ 13 to ↓ 40)  
C<sub>max</sub>: ↓ 13% (↓ 0 to ↓ 23)  
4-hydroxy atorvastatin:  
AUC: ↓ 4% (↓ 0 to ↓ 31)  
C<sub>max</sub>: ↓ 47% (↓ 9 to ↓ 51)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 34% (↓ 21 to ↓ 41)  
C<sub>max</sub>: ↓ 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<sub>max</sub>: ↓ 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| **Simvastatin/Efavirenz** *(40 mg once daily/600 mg once daily)* | Simvastatin:  
AUC: ↓ 69% (↓ 62 to ↓ 73)  
C<sub>max</sub>: ↓ 76% (↓ 63 to ↓ 79)  
Simvastatin acid:  
AUC: ↓ 58% (↓ 39 to ↓ 68)  
C<sub>max</sub>: ↓ 51% (↓ 32 to ↓ 58)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 60% (↓ 52 to ↓ 68)  
C<sub>max</sub>: ↓ 62% (↓ 55 to ↓ 78)  
(CYP3A4 induction)  
Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C<sub>max</sub> 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<sub>max</sub>: ↔  
C<sub>min</sub>: ↓ 8% (↑ 14 to ↓ 25)  
Norelgestromin (active metabolite):  
AUC: ↓ 64% (↓ 62 to ↓ 67)  
C<sub>max</sub>: ↓ 46% (↓ 39 to ↓ 52)  
C<sub>min</sub>: ↓ 82% (↓ 79 to ↓ 85)  
Levonorgestrel (active metabolite):  
AUC: ↓ 83% (↓ 79 to ↓ 87)  
C<sub>max</sub>: ↓ 80% (↓ 77 to ↓ 83)  
C<sub>min</sub>: ↓ 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** | Interaction not studied. 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)

<table>
<thead>
<tr>
<th>Effects on drug levels Mean percent change in AUC, C\text{max}, C\text{min} with confidence intervals if available(^a) (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| **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\text{max}: ↓ 45% (↓ 25 to ↓ 59) (CYP3A4 induction)
In a study of HIV infected intravenous drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. | Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms. |

Buprenorphine/naloxone/Efavirenz

Buprenorphine: AUC: ↓ 50%
Norbuprenorphine: AUC: ↓ 71%
Efavirenz: No clinically significant pharmacokinetic interaction

Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine or efavirenz may not be necessary when co-administered. |

\(^a\) 90% confidence intervals unless otherwise noted.
\(^b\) 95% confidence intervals.

### Paediatric population

Interaction studies have only been performed in adults.

### 4.6 Fertility, pregnancy and lactation

Efavirenz should not be used during pregnancy unless there are no other appropriate treatment options.

*Women of childbearing potential:* pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.

*Pregnancy:* there are limited amount of data from the use of efavirenz in pregnant women. In postmarketing experience through an antiretroviral pregnancy registry, outcomes for more than 400 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been prospectively reported with no specific malformation pattern observed. A small number of cases of neural tube defects, including meningomyelocele, have been reported via the registry. Most neural tube defects were isolated retrospectively reported cases, and causality cannot be
ruled out but has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects (see section 5.3).

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

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

#### a. Summary of the safety profile

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported adverse reactions of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most notable adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2 - 4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; psychiatric adverse reactions including severe depression, death by suicide, and psychosis like behaviour; and seizures have been reported in patients treated with efavirenz. The administration of SUSTIVA with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

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

#### b. Tabulated list of adverse reactions

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below. Also listed in italics are adverse reactions observed post-marketing in association with efavirenz-containing antiretroviral treatment regimens. Frequency is defined using the following convention: very common (≥ 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).

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td>hypersensitivity</td>
</tr>
</tbody>
</table>
### Psychiatric disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>common</strong></td>
<td>abnormal dreams, anxiety, depression, insomnia*</td>
</tr>
<tr>
<td><strong>uncommon</strong></td>
<td>affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis†, suicide attempt, suicide ideation*</td>
</tr>
<tr>
<td><strong>rare</strong></td>
<td>delusion†, neurosis‡, completed suicide‡*</td>
</tr>
</tbody>
</table>

### Nervous system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>common</strong></td>
<td>cerebellar coordination and balance disturbances†, disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%)*</td>
</tr>
<tr>
<td><strong>uncommon</strong></td>
<td>agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal, <em>tremor</em> ‡</td>
</tr>
</tbody>
</table>

### Eye disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>uncommon</strong></td>
<td>vision blurred</td>
</tr>
</tbody>
</table>

### Ear and labyrinth disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>uncommon</strong></td>
<td>tinnitus†, vertigo</td>
</tr>
</tbody>
</table>

### Vascular disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>uncommon</strong></td>
<td>flushing‡</td>
</tr>
</tbody>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>common</strong></td>
<td>abdominal pain, diarrhoea, nausea, vomiting</td>
</tr>
<tr>
<td><strong>uncommon</strong></td>
<td>pancreatitis</td>
</tr>
</tbody>
</table>

### Hepatobiliary disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>uncommon</strong></td>
<td>hepatitis acute</td>
</tr>
<tr>
<td><strong>rare</strong></td>
<td>hepatic failure‡*</td>
</tr>
</tbody>
</table>

### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>very common</strong></td>
<td>rash (11.6%)*</td>
</tr>
<tr>
<td><strong>common</strong></td>
<td>pruritus</td>
</tr>
<tr>
<td><strong>uncommon</strong></td>
<td>erythema multiforme, Stevens-Johnson syndrome*</td>
</tr>
<tr>
<td><strong>rare</strong></td>
<td>photoallergic dermatitis‡</td>
</tr>
</tbody>
</table>

### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>uncommon</strong></td>
<td>gynaecomastia</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>common</strong></td>
<td>fatigue</td>
</tr>
</tbody>
</table>

*See section c. Description of selected adverse reactions for more details.*
c. Description of selected adverse reactions

**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:

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz regimen (n=1,008)</th>
<th>Control regimen (n=635)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- severe depression</td>
<td>1.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>- suicidal ideation</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- non-fatal suicide attempts</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>- aggressive behaviour</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- paranoid reactions</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- manic reactions</td>
<td>0.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

**Nervous system symptoms:** in clinical controlled trials, frequently reported adverse reactions included, but were not limited to dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms of moderate-to-severe intensity were experienced by 19% (severe 2%) of patients compared to 9% (severe 1%) of patients receiving control regimens. In clinical studies 2% of patients treated with efavirenz discontinued therapy due to such symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Nervous system symptoms may occur more frequently when efavirenz is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms and can be recommended during the first weeks of therapy.
and in patients who continue to experience these symptoms (see section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit.

Analysis of long-term data showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the control arm.

Hepatic failure: A few of the 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 (see section 4.4).

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

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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

Laboratory test abnormalities:

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

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

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

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

d. Paediatric population

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

e. Other special populations

Liver enzymes in hepatitis B or C co-infected patients: in the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these 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).

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: 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).

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 medications used in combination with efavirenz.

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

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

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

Clinical efficacy:

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

Two controlled studies (006 and ACTG 364) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naïve and NRTI-experienced HIV-infected patients. Study 020 showed similar activity in NRTI-experienced patients over 24 weeks. In these studies the dose of efavirenz was 600 mg once daily; the dose of indinavir was 1,000 mg every 8 hours when used with efavirenz and 800 mg every 8 hours when used without efavirenz. The dose of nelfinavir was 750 mg given three times a day. The standard doses of NRTIs given every 12 hours were used in each of these studies.

Study 006, a randomized, open-label trial, compared efavirenz + zidovudine + lamivudine or efavirenz + indinavir with indinavir + zidovudine + lamivudine in 1,266 patients who were required to be efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The mean baseline CD4 cell count was 341 cells/mm³ and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>n</th>
<th>48 weeks</th>
<th>48 weeks</th>
<th>48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV + ZDV + 3TC</td>
<td>202</td>
<td>67%</td>
<td>62%</td>
<td>187</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(60%, 73%)</td>
<td>(55%, 69%)</td>
<td>(11.8)</td>
</tr>
<tr>
<td>EFV + IDV</td>
<td>206</td>
<td>54%</td>
<td>48%</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(47%, 61%)</td>
<td>(41%, 55%)</td>
<td>(11.3)</td>
</tr>
<tr>
<td>IDV + 3TC</td>
<td>206</td>
<td>45%</td>
<td>40%</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(38%, 52%)</td>
<td>(34%, 47%)</td>
<td>(12.3)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Number/ Treatment Regimens</th>
<th>n</th>
<th>% (95% C.I.)</th>
<th>% (95% C.I.)</th>
<th>Mean change from baseline-CD4 cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ACTG 364</td>
<td>48 weeks</td>
<td>&lt; 500 copies/ml</td>
<td>&lt; 50 copies/ml</td>
<td>---</td>
</tr>
<tr>
<td>EFV + NFV + NRTIs</td>
<td>65</td>
<td>70 (59, 82)</td>
<td>---</td>
<td>107 (17.9)</td>
</tr>
<tr>
<td>EFV + NRTIs</td>
<td>65</td>
<td>58 (46, 70)</td>
<td>---</td>
<td>114 (21.0)</td>
</tr>
<tr>
<td>NFV + NRTIs</td>
<td>66</td>
<td>30 (19, 42)</td>
<td>---</td>
<td>94 (13.6)</td>
</tr>
<tr>
<td>Study 020</td>
<td>24 weeks</td>
<td>&lt; 400 copies/ml</td>
<td>&lt; 50 copies/ml</td>
<td>---</td>
</tr>
<tr>
<td>EFV + IDV + NRTIs</td>
<td>157</td>
<td>60 (52, 68)</td>
<td>49 (41, 58)</td>
<td>104 (9.1)</td>
</tr>
<tr>
<td>IDV + NRTIs</td>
<td>170</td>
<td>51 (43, 59)</td>
<td>38 (30, 45)</td>
<td>77 (9.9)</td>
</tr>
</tbody>
</table>

a NC = F, noncompleter = failure.  
b EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir.  
c C.I., confidence interval for proportion of patients in response.  
d S.E.M., standard error of the mean.  
---, not performed.
**Paediatric population:** ACTG 382 is an ongoing uncontrolled study of 57 NRTI-experienced paediatric patients (3 - 16 years) which characterises the pharmacokinetics, antiviral activity and safety of efavirenz in combination with nelfinavir (20 - 30 mg/kg given three times a day) and one or more NRTIs. The starting dose of efavirenz was the equivalent of a 600 mg dose (adjusted from calculated body size based on weight). The response rate, based on the NC = F analysis of the percentage of patients with plasma HIV-RNA < 400 copies/ml at 48 weeks was 60% (95%, C.I. 47, 72), and 53% (C.I. 40, 66) based on percentage of patients with plasma HIV-RNA < 50 copies/ml. The mean CD4 cell counts were increased by 63 ± 34.5 cells/mm² from baseline. The durability of the response was similar to that seen in adult patients.

5.2 **Pharmacokinetic properties**

**Absorption:** peak efavirenz plasma concentrations of 1.6 - 9.1 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 P450 enzymes, resulting in the induction of its own metabolism. 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).

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

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

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

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

5.3 Preclinical safety data
Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays.

Efavirenz induced foetal resorptions in rats. Malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, microphthalmia 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
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)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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 hard capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/002 - bottle

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 May 1999
Date of latest renewal: 28 May 2009
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 200 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 200 mg of efavirenz.

Excipient: each hard capsule contains 114.0 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule

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 years of age and older.

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

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

4.2 **Posology and method of administration**

**Posology**

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

*Concomitant antiretroviral therapy:* SUSTIVA must be given in combination with other antiretroviral medicines (see section 4.5).

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

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

*Adults:* the recommended dose of SUSTIVA 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 SUSTIVA is coadministered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the SUSTIVA 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 SUSTIVA is coadministered with rifampicin, an increase in the dose of SUSTIVA 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 (3 to 17 years)
The recommended dose of SUSTIVA in combination with a PI and/or NRTIs for patients between 3 and 17 years of age is described in Table 1. SUSTIVA hard capsules must only be administered to children who are able to reliably swallow hard capsules. The safety and efficacy of SUSTIVA in children below the age of 3 years or weighing less than 13 kg have not yet been established (see sections 5.1 and 5.2).

Alternative method of administration: for children at least 3 years old and weighing at least 13 kg and adults who cannot reliably swallow hard capsules, SUSTIVA oral solution is the preferred formulation. Administration of the capsule contents with a small amount (1-2 teaspoons) of food may be considered for patients who cannot tolerate the oral solution. In a palatability study in healthy adults of efavirenz mixed with applesauce, grape jelly, yogurt, or infant formula, grape jelly received the highest rating of good overall taste. 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 vertically 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. There are limited safety and tolerability data for administration of the capsule contents in paediatric patients.

### Table 1
Paediatric dose to be administered once daily*

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to &lt; 15</td>
<td>200</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>250</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>300</td>
</tr>
<tr>
<td>25 to &lt; 32.5</td>
<td>350</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>400</td>
</tr>
<tr>
<td>≥ 40</td>
<td>600</td>
</tr>
</tbody>
</table>

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

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Class C) (see section 5.2).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects [for example, cardiac arrhythmias, prolonged sedation or respiratory depression] (see section 4.5).

Herbal preparations containing St. John’s wort (*Hypericum perforatum*) must not be used while taking efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

### 4.4 Special warnings and precautions for use

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance (see section 5.1).

Co-administration of efavirenz with the fixed combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate is not recommended.

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

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

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

*Rash*: mild-to-moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus (see section 4.8).

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

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

**Nervous system symptoms:** symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

**Seizures:** convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

**Hepatic events:** a few of the 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.

**Effect of food:** the administration of SUSTIVA 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 SUSTIVA 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.

**Lipodystrophy and metabolic abnormalities:** combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

**Osteonecrosis:** although the etiology 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 years of age or who weigh less than 13 kg. Therefore, efavirenz should not be given to children less than 3 years of age.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4 (see section 5.2). Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.

Contraindications of concomitant use

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

St. John’s wort (Hypericum perforatum): co-administration of efavirenz and St. John’s wort or herbal preparations containing St. John’s wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John’s wort due to induction of drug metabolising enzymes and/or transport
proteins by St. John’s wort. If a patient is already taking St. John’s wort, stop St. John’s wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John’s wort and the dose of efavirenz may need adjusting. The inducing effect of St. John’s wort may persist for at least 2 weeks after cessation of treatment. (see section 4.3).

**Other interactions**

Interactions between efavirenz and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in Table 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**

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C\text{max}, C\text{min} with confidence intervals if available(^a) (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Protease inhibitors (PI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/ritonavir/Efavirenz (400 mg once daily/100 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm): AUC: ↔, C\text{max}: ↑17%(^<em>) (↑8 to ↑27), C\text{min}: ↓42%(^</em>) (↓31 to ↓51)</td>
<td>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.</td>
</tr>
<tr>
<td>Atazanavir/ritonavir/Efavirenz (400 mg once daily/200 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm): AUC: ↔, C\text{max}: ↔, C\text{min}: ↑12%(^*) (↑16 to ↑49) (CYP3A4 induction). * When compared to atazanavir 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C\text{min} might negatively impact the efficacy of atazanavir. ** based on historical comparison</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir/Efavirenz (300 mg twice daily*/100 mg twice daily/600 mg once daily)</td>
<td>Darunavir: AUC: ↓13% C\text{min}: ↓31% (CYP3A4 induction) Efavirenz: AUC: ↑21% C\text{min}: ↑17% (CYP3A4 inhibition)</td>
<td>The clinical significance of the changes has not been established. Similar findings are expected with the approved darunavir/ritonavir 600/100 mg twice daily dose. This combination should be used with caution. See ritonavir row below.</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir/Efavirenz (700 mg twice daily/100 mg twice daily/600 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction</td>
<td>No dose adjustment is necessary for any of these medicinal products. See also ritonavir row below.</td>
</tr>
<tr>
<td>Fosamprenavir/Nelfinavir/Efavirenz</td>
<td>Interaction not studied.</td>
<td>No dose adjustment is necessary for any of these medicinal products.</td>
</tr>
<tr>
<td>Fosamprenavir/Saquinavir/Efavirenz</td>
<td>Interaction not studied.</td>
<td>Not recommended as the exposure to both PIs is expected to be significantly decreased.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available(^a) (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 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. |
| 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir/Efavirenz (500 mg twice daily/600 mg once daily)</td>
<td><strong>Ritonavir:</strong> Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔ Morning C&lt;sub&gt;max&lt;/sub&gt;: ↑ 24% (↑ 12 to ↑ 38) Evening C&lt;sub&gt;max&lt;/sub&gt;: ↔ Morning C&lt;sub&gt;min&lt;/sub&gt;: ↑ 42% (↑ 9 to ↑ 86) &lt;sup&gt;b&lt;/sup&gt; Evening C&lt;sub&gt;min&lt;/sub&gt;: ↑ 24% (↑ 3 to ↑ 50) &lt;sup&gt;b&lt;/sup&gt; <strong>Efavirenz:</strong> AUC: ↑ 21% (↑ 10 to ↑ 34) C&lt;sub&gt;max&lt;/sub&gt;: ↑ 14% (↑ 4 to ↑ 26) C&lt;sub&gt;min&lt;/sub&gt;: ↑ 25% (↑ 7 to ↑ 46) &lt;sup&gt;b&lt;/sup&gt; (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.</td>
<td>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.</td>
</tr>
<tr>
<td>Saquinavir/ritonavir/Efavirenz</td>
<td>Interaction not studied.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>CCR5 antagonist</strong></td>
<td></td>
<td>Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc.</td>
</tr>
<tr>
<td>Maraviroc/Efavirenz (100 mg twice daily/600 mg once daily)</td>
<td><strong>Maraviroc:</strong> AUC&lt;sub&gt;12&lt;/sub&gt;: ↓ 45% (↓ 38 to ↓ 51) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 51% (↓ 37 to ↓ 62) Efavirenz concentrations not measured, no effect is expected.</td>
<td></td>
</tr>
<tr>
<td><strong>Integrase strand transfer inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir/Efavirenz (400 mg single dose/-)</td>
<td><strong>Raltegravir:</strong> AUC: ↓ 36% C&lt;sub&gt;12&lt;/sub&gt;: ↓ 21% C&lt;sub&gt;max&lt;/sub&gt;: ↓ 36% (UGT1A1 induction)</td>
<td>No dose adjustment is necessary for raltegravir.</td>
</tr>
<tr>
<td><strong>NRTIs and NNRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTIs/Efavirenz</td>
<td>Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine, and tenofovir disoproxil fumarate. Clinically significant interactions are not expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>NNRTIs/Efavirenz</td>
<td>Interaction not studied.</td>
<td>Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of efavirenz</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C\textsubscript{max}, C\textsubscript{min} with confidence intervals if available\textsuperscript{a} (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
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</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin/Efavirenz (600 mg single dose/400 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
</tbody>
</table>
| Clarithromycin/Efavirenz (500 mg q12h/400 mg once daily) | Clarithromycin:  
AUC: ↓ 39\% (↓ 30 to ↓ 46)  
C\textsubscript{max}: ↓ 26\% (↓ 15 to ↓ 35)  
Clarithromycin 14-hydroxymetabolite:  
AUC: ↑ 34\% (↑ 18 to ↑ 53)  
C\textsubscript{max}: ↑ 49\% (↑ 32 to ↑ 69)  
Efavirenz:  
AUC: ↔  
C\textsubscript{max}: ↑ 11\% (↑ 3 to ↑ 19)  
(CYP3A4 induction)  
Rash developed in 46\% of uninfected volunteers receiving efavirenz and clarithromycin. | The clinical significance of these changes in clarithromycin plasma levels is not known.  
Alternatives to clarithromycin (e.g. azithromycin) may be considered. No dose adjustment is necessary for efavirenz. |
| Other macrolide antibiotics (e.g. erythromycin)/Efavirenz | Interaction not studied.                                                                                                                                                                                   | No data are available to make a dose recommendation.                                                                                                                                             |
| **Antimycobacterials**                       |                                                                                                                                                                                                          |                                                                                                                                                                                                          |
| Rifabutin/Efavirenz (300 mg once daily/600 mg once daily) | Rifabutin:  
AUC: ↓ 38\% (↓ 28 to ↓ 47)  
C\textsubscript{max}: ↓ 32\% (↓ 15 to ↓ 46)  
C\textsubscript{min}: ↓ 45\% (↓ 31 to ↓ 56)  
Efavirenz:  
AUC: ↔  
C\textsubscript{max}: ↔  
C\textsubscript{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. |                                                                                                                                                                                                          |
| Rifampicin/Efavirenz (600 mg once daily/600 mg once daily) | Efavirenz:  
AUC: ↓ 26\% (↓ 15 to ↓ 36)  
C\textsubscript{max}: ↓ 20\% (↓ 11 to ↓ 28)  
C\textsubscript{min}: ↓ 32\% (↓ 15 to ↓ 46)  
(CYP3A4 and CYP2B6 induction)  
When taken with rifampicin, 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. |                                                                                                                                                                                                          |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| Itraconazole/Efavirenz (200 mg q12h/600 mg once daily) | Itraconazole:  
AUC: ↓ 39% (↓ 21 to ↓ 53)  
C<sub>max</sub>: ↓ 37% (↓ 20 to ↓ 51)  
C<sub>min</sub>: ↓ 44% (↓ 27 to ↓ 58)  
(decrease in itraconazole concentrations: CYP3A4 induction)  
Hydroxyitraconazole:  
AUC: ↓ 37% (↓ 14 to ↓ 55)  
C<sub>max</sub>: ↓ 35% (↓ 12 to ↓ 52)  
C<sub>min</sub>: ↓ 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. |
| Posaconazole/Efavirenz --/400 mg once daily | Posaconazole:  
AUC: ↓ 50%  
C<sub>max</sub>: ↓ 45%  
(UDP-G induction) | Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk. |
| Voriconazole/Efavirenz (200 mg twice daily/400 mg once daily) | Voriconazole:  
AUC: ↓ 77%  
C<sub>max</sub>: ↓ 61%  
Efavirenz:  
AUC: ↑ 44%  
C<sub>max</sub>: ↑ 38%  
Voriconazole:  
AUC: ↓ 7% (↓ 23 to ↑ 13) *  
C<sub>max</sub>: ↑ 23% (↓ 1 to ↑ 53) *  
Efavirenz:  
AUC: ↑ 17% (↑ 6 to ↑ 29) **  
C<sub>max</sub>: ↔ **  
*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. |
<p>| 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. |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C\text{max}, C\text{min} with confidence intervals if available(^a) (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACID REDUCING AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminium hydroxide-magnesium hydroxide-simethicone antacid/Efavirenz (30 ml single dose/400 mg single dose)</td>
<td>Neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz.</td>
<td>Co-administration of efavirenz with medicinal products that alter gastric pH would not be expected to affect efavirenz absorption.</td>
</tr>
<tr>
<td>Famotidine/Efavirenz (40 mg single dose/400 mg single dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTIANXIETY AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam/Efavirenz (2 mg single dose/600 mg once daily)</td>
<td>Lorazepam: AUC: ↑ 7% (↑ 1 to ↑ 14) C\text{max}: ↑ 16% (↑ 2 to ↑ 32) These changes are not considered clinically significant.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin/Efavirenz</td>
<td>Interaction not studied. Plasma concentrations and effects of warfarin are potentially increased or decreased by efavirenz.</td>
<td>Dose adjustment of warfarin may be required.</td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine/Efavirenz (400 mg once daily/600 mg once daily)</td>
<td>Carbamazepine: AUC: ↓ 27% (↓ 20 to ↓ 33) C\text{max}: ↓ 20% (↓ 15 to ↓ 24) C\text{min}: ↓ 35% (↓ 24 to ↓ 44) Efavirenz: AUC: ↓ 36% (↓ 32 to ↓ 40) C\text{max}: ↓ 21% (↓ 15 to ↓ 26) C\text{min}: ↓ 47% (↓ 41 to ↓ 53) (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction) The steady-state AUC, C\text{max} and C\text{min} of the active carbamazepine epoxide metabolite remained unchanged. Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.</td>
<td>No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.</td>
</tr>
<tr>
<td>Phenytoin, Phenobarbital, and other anticonvulsants that are substrates of CYP450 isoenzymes</td>
<td>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.</td>
<td>When efavirenz is co-administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic monitoring of anticonvulsant levels should be conducted.</td>
</tr>
<tr>
<td>Valproic acid/Efavirenz (250 mg twice daily/600 mg once daily)</td>
<td>No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.</td>
<td>No dose adjustment is necessary for efavirenz. Patients should be monitored for seizure control.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Vigabatrin/Efavirenz Gabapentin/Efavirenz</td>
<td>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.</td>
<td>No dose adjustment is necessary for any of these medicinal products.</td>
</tr>
</tbody>
</table>

**ANTIDEPRESSANTS**

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

| Sertraline/Efavirenz (50 mg once daily/600 mg once daily) | Sertraline:  
AUC: ↓ 39% (↓ 27 to ↓ 50)  
C<sub>max</sub>: ↓ 29% (↓ 15 to ↓ 40)  
C<sub>min</sub>: ↓ 46% (↓ 31 to ↓ 58)  
Efavirenz:  
AUC: ↔  
C<sub>max</sub>: ↑ 11% (↑ 6 to ↑ 16)  
C<sub>min</sub>: ↔ (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. |

**ANTIHISTAMINES**

| Cetirizine/Efavirenz (10 mg single dose/600 mg once daily) | Cetirizine:  
AUC: ↔  
C<sub>max</sub>: ↓ 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARDIOVASCULAR AGENTS</strong></td>
<td><strong>Calcium Channel Blockers</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>
| Diltiazem/Efavirenz (240 mg once daily/600 mg once daily) | Diltiazem:  
AUC: ↓ 69% (↓ 55 to ↓ 79)  
C<sub>max</sub>: ↓ 60% (↓ 50 to ↓ 68)  
C<sub>min</sub>: ↓ 63% (↓ 44 to ↓ 75)  
Desacetyl diltiazem:  
AUC: ↓ 75% (↓ 59 to ↓ 84)  
C<sub>max</sub>: ↓ 64% (↓ 57 to ↓ 69)  
C<sub>min</sub>: ↓ 62% (↓ 44 to ↓ 75)  
N-monodesmethyl diltiazem:  
AUC: ↓ 37% (↓ 17 to ↓ 52)  
C<sub>max</sub>: ↓ 28% (↓ 7 to ↓ 44)  
C<sub>min</sub>: ↓ 37% (↓ 17 to ↓ 52)  
Efavirenz:  
AUC: ↑ 11% (↑ 5 to ↑ 18)  
C<sub>max</sub>: ↑ 16% (↑ 6 to ↑ 26)  
C<sub>min</sub>: ↑ 13% (↑ 1 to ↑ 26)  
(CYP3A4 induction)  
The increase in efavirenz pharmacokinetic parameters is not considered clinically significant. | Dose adjustments of calcium channel blockers should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker). |
| 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. | |
| **LIPID LOWERING MEDICINAL PRODUCTS**       | **HMG Co-A Reductase Inhibitors**                                                                                     | 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. |
| Atorvastatin/Efavirenz (10 mg once daily/600 mg once daily) | Atorvastatin:  
AUC: ↓ 43% (↓ 34 to ↓ 50)  
C<sub>max</sub>: ↓ 12% (↓ 1 to ↓ 26)  
2-hydroxy atorvastatin:  
AUC: ↓ 35% (↓ 13 to ↓ 40)  
C<sub>max</sub>: ↓ 13% (↓ 0 to ↓ 23)  
4-hydroxy atorvastatin:  
AUC: ↓ 1% (↓ 0 to ↓ 9)  
C<sub>max</sub>: ↓ 47% (↓ 9 to ↓ 51)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 34% (↓ 21 to ↓ 41)  
C<sub>max</sub>: ↓ 20% (↓ 2 to ↓ 26) | |
| Pravastatin/Efavirenz (40 mg once daily/600 mg once daily) | Pravastatin:  
AUC: ↓ 40% (↓ 26 to ↓ 57)  
C<sub>max</sub>: ↓ 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| Simvastatin/Efavirenz (40 mg once daily/600 mg once daily) | Simvastatin:  
AUC: ↓ 69% (↓ 62 to ↓ 73)  
C<sub>max</sub>: ↓ 76% (↓ 63 to ↓ 79)  
Simvastatin acid:  
AUC: ↓ 58% (↓ 39 to ↓ 68)  
C<sub>max</sub>: ↓ 51% (↓ 32 to ↓ 58)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 60% (↓ 52 to ↓ 68)  
C<sub>max</sub>: ↓ 62% (↓ 55 to ↓ 78)  
(CYP3A4 induction)  
Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C<sub>max</sub> 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. |
<p>| 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. |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HORMONAL CONTRACEPTIVES</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Oral: Ethinyloestradiol + Norgestimate/ Efavirenz (0.035 mg + 0.25 mg once daily/600 mg once daily) | Ethinyloestradiol:  
AUC: ↔  
C<sub>max</sub>: ↔  
C<sub>min</sub>: ↓ 8% (↑ 14 to ↓ 25)  
Norelgestromin (active metabolite):  
AUC: ↓ 64% (↓ 62 to ↓ 67)  
C<sub>max</sub>: ↓ 46% (↓ 39 to ↓ 52)  
C<sub>min</sub>: ↓ 82% (↓ 79 to ↓ 85)  
Levonorgestrel (active metabolite):  
AUC: ↓ 83% (↓ 79 to ↓ 87)  
C<sub>max</sub>: ↓ 80% (↓ 77 to ↓ 83)  
C<sub>min</sub>: ↓ 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). |
<p>| 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 | Interaction not studied. 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). |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, $C_{\text{max}}$, $C_{\text{min}}$ with confidence intervals if available$^a$ (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMUNOSUPPRESSANTS</td>
<td>Interaction not studied. Decreased exposure of the immunosuppressant may be expected (CYP3A4 induction). These immunosuppressants are not anticipated to affect exposure of efavirenz.</td>
<td>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.</td>
</tr>
<tr>
<td>Immunosuppressants metabolized by CYP3A4 (eg, cyclosporine, tacrolimus, sirolimus)/Efavirenz</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| OPIOIDS                                      | Methadone:  
AUC: ↓ 52% (↓ 33 to ↓ 66)  
$C_{\text{max}}$: ↓ 45% (↓ 25 to ↓ 59) (CYP3A4 induction)  
In a study of HIV infected intravenous drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms.  
Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms. |                                                                                                           |
| Methadone/Efavirenz (stable maintenance, 35-100 mg once daily/600 mg once daily) |                                                                                                                   |                                                                                                           |
| 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.

**Paediatric population**

Interaction studies have only been performed in adults.

### 4.6 Fertility, pregnancy and lactation

Efavirenz should not be used during pregnancy unless there are no other appropriate treatment options.

**Women of childbearing potential:** pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.

**Pregnancy:** there are limited amount of data from the use of efavirenz in pregnant women. In postmarketing experience through an antiretroviral pregnancy registry, outcomes for more than 400 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been prospectively reported with no specific malformation pattern observed. A small number of cases of neural tube defects, including meningomyelocele, have been reported via the registry. Most neural tube defects were isolated retrospectively reported cases, and causality cannot be
ruled out but has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects (see section 5.3).

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

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

#### a. Summary of the safety profile

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported adverse reactions of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most notable adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2 - 4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; psychiatric adverse reactions including severe depression, death by suicide, and psychosis like behaviour; and seizures have been reported in patients treated with efavirenz. The administration of SUSTIVA with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

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

#### b. Tabulated list of adverse reactions

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below. Also listed in italics are adverse reactions observed post-marketing in association with efavirenz-containing antiretroviral treatment regimens. Frequency is defined using the following convention: very common (≥ 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).

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>common</strong></td>
<td>abnormal dreams, anxiety, depression, insomnia*</td>
</tr>
<tr>
<td><strong>uncommon</strong></td>
<td>affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis†, suicide attempt, suicide ideation*</td>
</tr>
<tr>
<td><strong>rare</strong></td>
<td><em>delusion†, neurosis‡, completed suicide‡</em></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>common</td>
<td><em>cerebellar coordination and balance disturbances</em>, disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%)*</td>
</tr>
<tr>
<td>uncommon</td>
<td>agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal, *tremor†</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>vision blurred</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td><em>tinnitus</em>, vertigo</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td><em>flushing</em></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>common</td>
<td>abdominal pain, diarrhoea, nausea, vomiting</td>
</tr>
<tr>
<td>uncommon</td>
<td>pancreatitis</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>hepatitis acute</td>
</tr>
<tr>
<td>rare</td>
<td><em>hepatic failure‡</em></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>very common</strong></td>
<td><em>rash</em> (11.6%)*</td>
</tr>
<tr>
<td><strong>common</strong></td>
<td>pruritus</td>
</tr>
<tr>
<td><strong>uncommon</strong></td>
<td>erythema multiforme, Stevens-Johnson syndrome*</td>
</tr>
<tr>
<td><strong>rare</strong></td>
<td><em>photoallergic dermatitis</em>†</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>gynaecomastia</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>common</strong></td>
<td>fatigue</td>
</tr>
</tbody>
</table>

*See section c. Description of selected adverse reactions for more details.*
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).

c. Description of selected adverse reactions

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:

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz regimen</th>
<th>Control regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1,008)</td>
<td>(n=635)</td>
</tr>
<tr>
<td>severe depression</td>
<td>1.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>suicidal ideation</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>non-fatal suicide attempts</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>aggressive behaviour</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>paranoid reactions</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>manic reactions</td>
<td>0.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

Nervous system symptoms: in clinical controlled trials, frequently reported adverse reactions included, but were not limited to dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms of moderate-to-severe intensity were experienced by 19% (severe 2%) of patients compared to 9% (severe 1%) of patients receiving control regimens. In clinical studies 2% of patients treated with efavirenz discontinued therapy due to such symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Nervous system symptoms may occur more frequently when efavirenz is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms and can be recommended during the first weeks of therapy.
and in patients who continue to experience these symptoms (see section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit.

Analysis of long-term data showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the control arm.

**Hepatic failure:** A few of the 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 (see section 4.4).

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

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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

**Laboratory test abnormalities:**

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

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

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

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

d. Paediatric population

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

e. Other special populations

Liver enzymes in hepatitis B or C co-infected patients: in the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these 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 liver disorders (see section 4.4).

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: 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).

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 medications used in combination with efavirenz.

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

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

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

Clinical efficacy:

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

Two controlled studies (006 and ACTG 364) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naïve and NRTI-experienced HIV-infected patients. Study 020 showed similar activity in NRTI-experienced patients over 24 weeks. In these studies the dose of efavirenz was 600 mg once daily; the dose of indinavir was 1,000 mg every 8 hours when used with efavirenz and 800 mg every 8 hours when used without efavirenz. The dose of nelfinavir was 750 mg given three times a day. The standard doses of NRTIs given every 12 hours were used in each of these studies.

Study 006, a randomized, open-label trial, compared efavirenz + zidovudine + lamivudine or efavirenz + indinavir with indinavir + zidovudine + lamivudine in 1,266 patients who were required to be efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The mean baseline CD4 cell count was 341 cells/mm³ and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>n</th>
<th>48 weeks</th>
<th>48 weeks</th>
<th>48 weeks</th>
<th>Mean change from baseline-CD4 cell count (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFV + ZDV + 3TC</strong></td>
<td>202</td>
<td>67% (60%, 73%)</td>
<td>62% (55%, 69%)</td>
<td>187 (11.8)</td>
<td></td>
</tr>
<tr>
<td><strong>EFV + IDV</strong></td>
<td>206</td>
<td>54% (47%, 61%)</td>
<td>48% (41%, 55%)</td>
<td>177 (11.3)</td>
<td></td>
</tr>
<tr>
<td><strong>IDV + ZDV + 3TC</strong></td>
<td>206</td>
<td>45% (38%, 52%)</td>
<td>40% (34%, 47%)</td>
<td>153 (12.3)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Number/Treatment Regimens</th>
<th>n</th>
<th>% (95% C.I.)</th>
<th>% (95% C.I.)</th>
<th>Mean change from baseline-CD4 cell count (S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study ACTG 364</strong></td>
<td>&lt; 500 copies/ml</td>
<td>&lt; 50 copies/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 weeks</td>
<td>65</td>
<td>70 (59, 82)</td>
<td>---</td>
<td>107 (17.9)</td>
</tr>
<tr>
<td>EFV + NFV + NRTIs</td>
<td>65</td>
<td>58 (46, 70)</td>
<td>---</td>
<td>114 (21.0)</td>
</tr>
<tr>
<td>EFV + NRTIs</td>
<td>66</td>
<td>30 (19, 42)</td>
<td>---</td>
<td>94 (13.6)</td>
</tr>
<tr>
<td><strong>Study 020</strong></td>
<td>&lt; 400 copies/ml</td>
<td>&lt; 50 copies/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>157</td>
<td>60 (52, 68)</td>
<td>49 (41, 58)</td>
<td>104 (9.1)</td>
</tr>
<tr>
<td>EFV + IDV + NRTIs</td>
<td>170</td>
<td>51 (43, 59)</td>
<td>38 (30, 45)</td>
<td>77 (9.9)</td>
</tr>
<tr>
<td>IDV + NRTIs</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

a NC = F, noncompleter = failure.
b EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir.
c C.I., confidence interval for proportion of patients in response.
d S.E.M., standard error of the mean.
---, not performed.
Paediatric population: ACTG 382 is an ongoing uncontrolled study of 57 NRTI-experienced paediatric patients (3 - 16 years) which characterises the pharmacokinetics, antiviral activity and safety of efavirenz in combination with nelfinavir (20 - 30 mg/kg given three times a day) and one or more NRTIs. The starting dose of efavirenz was the equivalent of a 600 mg dose (adjusted from calculated body size based on weight). The response rate, based on the NC = F analysis of the percentage of patients with plasma HIV-RNA < 400 copies/ml at 48 weeks was 60% (95%, C.I. 47, 72), and 53% (C.I. 40, 66) based on percentage of patients with plasma HIV-RNA < 50 copies/ml. The mean CD4 cell counts were increased by 63 ± 34.5 cells/mm³ from baseline. The durability of the response was similar to that seen in adult patients.

5.2 Pharmacokinetic properties

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

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

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 P450 enzymes, resulting in the induction of its own metabolism. 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).

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

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

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

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

### 5.3 Preclinical safety data
Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays.

Efavirenz induced foetal resorptions in rats. Malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, 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

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

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

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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/003 - bottle
EU/1/99/110/004 - blister
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 May 1999
Date of latest renewal: 28 May 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site:
1. **NAME OF THE MEDICINAL PRODUCT**

SUSTIVA 30 mg/ml oral solution

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml contains 30 mg of efavirenz

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Oral solution

Colourless to slightly yellow clear liquid.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

SUSTIVA oral solution is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 years of age and older, who are unable to swallow the hard capsules or the film-coated tablets.

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

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

4.2 **Posology and method of administration**

**Posology**

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

*Concomitant antiretroviral therapy:* SUSTIVA must be given in combination with other antiretroviral medicines (see section 4.5).

SUSTIVA oral solution may be taken with or without food (see section 5.2).

In order to improve the tolerability of nervous system undesirable effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms (see section 4.8).

*Adults:* the recommended dose of SUSTIVA in combination with nucleoside analogue reverse transcriptase inhibitors (NRTIs) with or without a PI (see section 4.5) is 24 ml orally, once daily.

*Dose adjustment:* If SUSTIVA is coadministered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the SUSTIVA 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 SUSTIVA is coadministered with rifampicin, an increase in the dose of SUSTIVA 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 (3 to 17 years)**
The recommended dose of SUSTIVA oral solution in combination with a PI and/or NRTIs for patients between 3 and 17 years of age is described in Table 1. SUSTIVA hard capsules or film-coated tablets must only be administered to children who are able to reliably swallow capsules or tablets. The safety and efficacy of SUSTIVA in children below the age of 3 years or weighing less than 13 kg have not yet been established (see sections 5.1 and 5.2).

**Table 1**
**Paediatric dose of SUSTIVA oral solution to be administered once daily**

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA oral solution (30 mg/ml) Dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children 3 - &lt; 5 years</td>
</tr>
<tr>
<td>13 to &lt; 15</td>
<td>12</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>13</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>15</td>
</tr>
<tr>
<td>25 to &lt; 32.5</td>
<td>17</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>-</td>
</tr>
<tr>
<td>≥ 40</td>
<td>-</td>
</tr>
</tbody>
</table>

SUSTIVA oral solution is less bioavailable than the hard capsule on a mg per mg basis. The dose recommendations in Table 1 have been adjusted to take into account the difference in bioavailability (see section 5.2).

**Alternative method of administration:** SUSTIVA oral solution is the preferred formulation for patients who cannot reliably swallow capsules or tablets. Administration of the capsule contents with a small amount (1-2 teaspoons) of food may be considered for patients who cannot tolerate the oral solution (see Table 2 and the Summary of Product Characteristics for SUSTIVA hard capsules). In a palatability study in healthy adults of efavirenz mixed with applesauce, grape jelly, yogurt, or infant formula, grape jelly received the highest rating of good overall taste. 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 vertically 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. There are limited safety and tolerability data for administration of the capsule contents in paediatric patients.

**Table 2**
**Paediatric dose of SUSTIVA hard capsules to be administered once daily**

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA hard capsules (30 mg) Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children 3 - &lt; 5 years</td>
</tr>
<tr>
<td>13 to &lt; 15</td>
<td>12</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>13</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>15</td>
</tr>
<tr>
<td>25 to &lt; 32.5</td>
<td>17</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>-</td>
</tr>
<tr>
<td>≥ 40</td>
<td>-</td>
</tr>
</tbody>
</table>
4.3 Contraindications

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

Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Class C) (see section 5.2).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozone, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects [for example, cardiac arrhythmias, prolonged sedation or respiratory depression] (see section 4.5).

Herbal preparations containing St. John’s wort (Hypericum perforatum) must not be used while taking efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

4.4 Special warnings and precautions for use

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance (see section 5.1).

Co-administration of efavirenz with the fixed combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate is not recommended.

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

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

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

Rash: mild-to-moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to &lt; 15</td>
<td>200</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>250</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>300</td>
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<tr>
<td>25 to &lt; 32.5</td>
<td>350</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>400</td>
</tr>
<tr>
<td>≥ 40</td>
<td>600</td>
</tr>
</tbody>
</table>

*For information on the bioavailability of the capsule contents mixed with food vehicles, see section 5.2.*
ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus (see section 4.8).

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

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

**Nervous system symptoms:** symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

**Seizures:** convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

**Hepatic events:** a few of the 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.

**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.

**Lipodystrophy and metabolic abnormalities:** combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).
**Osteonecrosis:** although the etiology 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 years of age or who weigh less than 13 kg. Evidence exists indicating that efavirenz may have altered pharmacokinetics in very young children. For this reason, efavirenz oral solution should not be given to children less than 3 years of age.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4 (see section 5.2). Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.
**Contraindications of concomitant use**

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

**St. John’s wort (Hypericum perforatum):** co-administration of efavirenz and St. John’s wort or herbal preparations containing St. John’s wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John’s wort due to induction of drug metabolising enzymes and/or transport proteins by St. John’s wort. If a patient is already taking St. John’s wort, stop St. John’s wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John’s wort and the dose of efavirenz may need adjusting. The inducing effect of St. John’s wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

**Other interactions**

Interactions between efavirenz and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in Table 3 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 3: Interactions between efavirenz and other medicinal products**

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors (PI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/ritonavir/Efavirenz (400 mg once daily/100 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm):</td>
<td>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.</td>
</tr>
<tr>
<td>Atazanavir/ritonavir/Efavirenz (400 mg once daily/200 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm):</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir/Efavirenz (300 mg twice daily*/100 mg twice daily/600 mg once daily)</td>
<td>Darunavir:</td>
<td>The clinical significance of the changes has not been established. Similar findings are expected with the approved darunavir/ritonavir 600/100 mg twice daily dose. This combination should be used with caution. See ritonavir row below.</td>
</tr>
</tbody>
</table>

*lower than recommended dose
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosamprenavir/ritonavir/Efavirenz (700 mg twice daily/100 mg twice daily/600 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction</td>
<td>No dose adjustment is necessary for any of these medicinal products. See also ritonavir row below.</td>
</tr>
<tr>
<td>Fosamprenavir/Nelfinavir/Efavirenz</td>
<td>Interaction not studied</td>
<td>No dose adjustment is necessary for any of these medicinal products. Not recommended as the exposure to both PIs is expected to be significantly decreased.</td>
</tr>
<tr>
<td>Fosamprenavir/Saquinavir/Efavirenz</td>
<td>Interaction not studied</td>
<td></td>
</tr>
</tbody>
</table>
| Indinavir/Efavirenz (800 mg q8h/200 mg once daily) | Indinavir:  
AUC: ↓ 31% (↓ 8 to ↓ 47)  
C<sub>min</sub>: ↓ 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)<sup>b</sup>  
C<sub>max</sub>: ↓ 17% (↓ 6 to ↓ 26)<sup>b</sup>  
C<sub>min</sub>: ↓ 50% (↓ 40 to ↓ 59)<sup>b</sup>  
Efavirenz:  
No clinically significant pharmacokinetic interaction  
The geometric mean C<sub>min</sub> for indinavir (0.33 mg/l) when given with ritonavir and efavirenz was higher than the mean historical C<sub>min</sub> (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. |
| Lopinavir/ritonavir soft capsules or oral solution/Efavirenz | 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nelfinavir/Efavirenz</strong> (750 mg q8h/600 mg once daily)</td>
<td>Nelfinavir: AUC: ↑ 20% (↑ 8 to ↑ 34) C&lt;sub&gt;max&lt;/sub&gt;: ↑ 21% (↑ 10 to ↑ 33) The combination was generally well tolerated.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td><strong>Ritonavir/Efavirenz</strong> (500 mg twice daily/600 mg once daily)</td>
<td>Ritonavir: Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔ Morning C&lt;sub&gt;max&lt;/sub&gt;: ↑ 24% (↑ 12 to ↑ 38) Evening C&lt;sub&gt;max&lt;/sub&gt;: ↔ Morning C&lt;sub&gt;min&lt;/sub&gt;: ↑ 42% (↑ 9 to ↑ 86)&lt;sup&gt;b&lt;/sup&gt; Evening C&lt;sub&gt;min&lt;/sub&gt;: ↑ 24% (↑ 3 to ↑ 50)&lt;sup&gt;b&lt;/sup&gt; Efavirenz: AUC: ↑ 21% (↑ 10 to ↑ 34) C&lt;sub&gt;max&lt;/sub&gt;: ↑ 14% (↑ 4 to ↑ 26) C&lt;sub&gt;min&lt;/sub&gt;: ↑ 25% (↑ 7 to ↑ 46)&lt;sup&gt;b&lt;/sup&gt; (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.</td>
<td>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.</td>
</tr>
<tr>
<td>Saquinavir/ritonavir/Efavirenz</td>
<td>Interaction not studied.</td>
<td>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.</td>
</tr>
</tbody>
</table>

**CCR5 antagonist**

| Maraviroc/Efavirenz (100 mg twice daily/600 mg once daily) | Maraviroc: AUC<sub>12</sub>: ↓ 45% (↓ 38 to ↓ 51) C<sub>max</sub>: ↓ 51% (↓ 37 to ↓ 62) Efavirenz concentrations not measured, no effect is expected. | Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc. |

**Integrase strand transfer inhibitor**

| Raltegravir/Efavirenz (400 mg single dose/ -) | Raltegravir: AUC: ↓ 36% C<sub>12</sub>: ↓ 21% C<sub>max</sub>: ↓ 36% (UGT1A1 induction) | No dose adjustment is necessary for raltegravir. |

**NRTIs and NNRTIs**

<p>| NRTIs/Efavirenz | Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine, and tenofovir disoproxil fumarate. Clinically significant interactions are not expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination | No dose adjustment is necessary for either medicinal product. |</p>
<table>
<thead>
<tr>
<th>medicinal product by therapeutic areas (dose)</th>
<th>effects on drug levels</th>
<th>recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTIs/Efavirenz</td>
<td>Interaction not studied.</td>
<td>Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of efavirenz and another NNRTI is not recommended.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin/Efavirenz (600 mg single dose/400 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>Clarithromycin/Efavirenz (500 mg q12h/400 mg once daily)</td>
<td>Clarithromycin: AUC: ↓ 39% (↓ 30 to ↓ 46) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 26% (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34% (↑ 18 to ↑ 53) C&lt;sub&gt;max&lt;/sub&gt;: ↑ 49% (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ C&lt;sub&gt;max&lt;/sub&gt;: ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin.</td>
<td>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.</td>
</tr>
<tr>
<td>Other macrolide antibiotics (e.g.,erythromycin)/Efavirenz</td>
<td>Interaction not studied.</td>
<td>No data are available to make a dose recommendation.</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin/Efavirenz (300 mg once daily/600 mg once daily)</td>
<td>Rifabutin: AUC: ↓ 38% (↓ 28 to ↓ 47) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 32% (↓ 15 to ↓ 46) C&lt;sub&gt;min&lt;/sub&gt;: ↓ 45% (↓ 31 to ↓ 56) Efavirenz: AUC: ↔ C&lt;sub&gt;max&lt;/sub&gt;: ↔ C&lt;sub&gt;min&lt;/sub&gt;: ↓ 12% (↓ 24 to ↑ 1) (CYP3A4 induction)</td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin/Efavirenz (600 mg once daily/600 mg once daily)</td>
<td>Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 20% (↓ 11 to ↓ 28) C&lt;sub&gt;min&lt;/sub&gt;: ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)</td>
<td>When taken with rifampicin, 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.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, $C_{\text{max}}$, $C_{\text{min}}$ with confidence intervals if availablea (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
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<tr>
<td><strong>Antifungals</strong></td>
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</tbody>
</table>
| Itraconazole/Efavirenz (200 mg q12h/600 mg once daily) | Itraconazole:  
AUC: ↓ 39% (↓ 21 to ↓ 53)  
$C_{\text{max}}$: ↓ 37% (↓ 20 to ↓ 51)  
$C_{\text{min}}$: ↓ 44% (↓ 27 to ↓ 58)  
(decrease in itraconazole concentrations: CYP3A4 induction)  
Hydroxyitraconazole:  
AUC: ↓ 37% (↓ 14 to ↓ 55)  
$C_{\text{max}}$: ↓ 35% (↓ 12 to ↓ 52)  
$C_{\text{min}}$: ↓ 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Posaconazole/Efavirenz ~--/400 mg once daily | Posaconazole:  
AUC: ↓ 50%  
$C_{\text{max}}$: ↓ 45%  
(UDP-G induction) | Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Voriconazole/Efavirenz (200 mg twice daily/400 mg once daily) | Voriconazole:  
AUC: ↓ 77%  
$C_{\text{max}}$: ↓ 61%  
Efavirenz:  
AUC: ↑ 44%  
$C_{\text{max}}$: ↑ 38%  
Voriconazole:  
AUC: ↓ 7% (↓ 23 to ↑ 13) *  
$C_{\text{max}}$: ↑ 23% (↓ 1 to ↑ 53) *  
Efavirenz:  
AUC: ↑ 17% (↑ 6 to ↑ 29) **  
$C_{\text{max}}$: ↔ **  
*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.                                                                                                                                                                                                                     |
| Voriconazole/Efavirenz (400 mg twice daily/300 mg once daily) | No clinically significant pharmacokinetic interaction | No dose adjustment is necessary for either medicinal product.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Fluconazole/Efavirenz (200 mg once daily/400 mg once daily) | No data are available to make a dose recommendation. | No dose adjustment is necessary for either medicinal product.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Ketoconazole and other imidazole antifungals | Interaction not studied | No dose adjustment is necessary for either medicinal product.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| **ACID REDUCING AGENTS**                   | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 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) | | |
| **ANTIANXIETY AGENTS**                     | Lorazepam:  
AUC: ↑ 7% (↑ 1 to ↑ 14)  
$C_{\text{max}}$: ↑ 16% (↑ 2 to ↑ 32)  
These changes are not considered clinically significant. | No dose adjustment is necessary for either medicinal product.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
<p>| Lorazepam/Efavirenz (2 mg single dose/600 mg once daily) | | |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>

**ANTICOAGULANTS**

- **Warfarin/Efavirenz**
  - Interaction not studied. Plasma concentrations and effects of warfarin are potentially increased or decreased by efavirenz.
  - Dose adjustment of warfarin may be required.

**ANTICONVULSANTS**

- **Carbamazepine/Efavirenz**
  - Carbamazepine:
    - AUC: ↓ 27% (↓ 20 to ↓ 33)
    - C<sub>max</sub>: ↓ 20% (↓ 15 to ↓ 24)
    - C<sub>min</sub>: ↓ 35% (↓ 24 to ↓ 44)
  - Efavirenz:
    - AUC: ↓ 36% (↓ 32 to ↓ 40)
    - C<sub>max</sub>: ↓ 21% (↓ 15 to ↓ 26)
    - C<sub>min</sub>: ↓ 47% (↓ 41 to ↓ 53)
  - (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction)
  - The steady-state AUC, C<sub>max</sub> and C<sub>min</sub> of the active carbamazepine epoxide metabolite remained unchanged.
  - Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.

- **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.
  - No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.

- **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 either medicinal product.

- **Vigabatrin/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<sub>max</sub>: ↓ 29% (↓ 15 to ↓ 40)
    - C<sub>min</sub>: ↓ 46% (↓ 31 to ↓ 58)
  - Efavirenz:
    - AUC: ↔
    - C<sub>max</sub>: ↑ 11% (↑ 6 to ↑ 16)
    - C<sub>min</sub>: ↔
    - (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.
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C\text{max}, C\text{min} with confidence intervals if availablea (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine/Efavirenz</td>
<td>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.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td><strong>ANTIHISTAMINES</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Cetirizine/Efavirenz                        | Cetirizine:  
AUC: ↔  
C\text{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. |
| (10 mg single dose/600 mg once daily)        |                                                                                                                                  |                                                             |
| **CARDIOVASCULAR AGENTS**                   |                                                                                                                                  |                                                             |
| Calcium Channel Blockers                    |                                                                                                                                  |                                                             |
| Diltiazem/Efavirenz                         | Diltiazem:  
AUC: ↓ 69% (↓ 55 to ↓ 79)  
C\text{max}: ↓ 60% (↓ 50 to ↓ 68)  
C\text{min}: ↓ 63% (↓ 44 to ↓ 75)  
Desacetyl diltiazem:  
AUC: ↓ 75% (↓ 59 to ↓ 84)  
C\text{max}: ↓ 64% (↓ 57 to ↓ 69)  
C\text{min}: ↓ 62% (↓ 44 to ↓ 75)  
N-monodesmethyl diltiazem:  
AUC: ↓ 37% (↓ 17 to ↓ 52)  
C\text{max}: ↓ 28% (↓ 7 to ↓ 44)  
C\text{min}: ↓ 37% (↓ 17 to ↓ 52)  
Efavirenz:  
AUC: ↑ 11% (↑ 5 to ↑ 18)  
C\text{max}: ↑ 16% (↑ 6 to ↑ 26)  
C\text{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. |
<p>| (240 mg once daily/600 mg once daily)        |                                                                                                                                  |                                                             |
| 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). |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIPID LOWERING MEDICINAL PRODUCTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG Co-A Reductase Inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Atorvastatin/Efavirenz (10 mg once daily/600 mg once daily) | Atorvastatin:  
AUC: ↓ 43% (↓ 34 to ↓ 50)  
C<sub>max</sub>: ↓ 12% (↓ 1 to ↓ 26)  
2-hydroxy atorvastatin:  
AUC: ↓ 35% (↓ 13 to ↓ 40)  
C<sub>max</sub>: ↓ 13% (↓ 0 to ↓ 23)  
4-hydroxy atorvastatin:  
AUC: ↓ 4% (↓ 0 to ↓ 31)  
C<sub>max</sub>: ↓ 47% (↓ 9 to ↓ 51)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 34% (↓ 21 to ↓ 41)  
C<sub>max</sub>: ↓ 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<sub>max</sub>: ↓ 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. |
| Simvastatin/Efavirenz (40 mg once daily/600 mg once daily) | Simvastatin:  
AUC: ↓ 69% (↓ 62 to ↓ 73)  
C<sub>max</sub>: ↓ 76% (↓ 63 to ↓ 79)  
Simvastatin acid:  
AUC: ↓ 58% (↓ 39 to ↓ 68)  
C<sub>max</sub>: ↓ 51% (↓ 32 to ↓ 58)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 60% (↓ 52 to ↓ 68)  
C<sub>max</sub>: ↓ 62% (↓ 55 to ↓ 78)  
(CYP3A4 induction)  
Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C<sub>max</sub> 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. |
<p>| 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. |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HORMONAL CONTRACEPTIVES</strong></td>
<td>Ethinyloestradiol:</td>
<td>A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).</td>
</tr>
<tr>
<td>Oral: Ethinyloestradiol + Norgestimate/ Efavirenz (0.035 mg + 0.25 mg once daily/600 mg once daily)</td>
<td>AUC: ↔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: ↔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt;: ↓ 8% (↑ 14 to ↓ 25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Norelgestromin (active metabolite):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC: ↓ 64% (↓ 62 to ↓ 67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: ↓ 46% (↓ 39 to ↓ 52)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt;: ↓ 82% (↓ 79 to ↓ 85)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethinyloestradiol:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC: ↔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: ↔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt;: ↓ 82% (↑ 14 to ↓ 25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efavirenz: no clinically significant interaction.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The clinical significance of these effects is not known.</td>
<td></td>
</tr>
<tr>
<td>Injection: Depomedroxyprogesterone acetate (DMPA)/Efavirenz (150 mg IM single dose DMPA)</td>
<td>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.</td>
<td>Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).</td>
</tr>
<tr>
<td>Implant: Etonogestrel/Efavirenz</td>
<td>Interaction not studied. Decreased exposure of etonogestrel may be expected (CYP3A4 induction). There have been occasional postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.</td>
<td>A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>IMMUNOSUPPRESSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressants metabolized by CYP3A4 (eg, cyclosporine, tacrolimus, sirolimus)/Efavirenz</td>
<td>Interaction not studied. Decreased exposure of the immunosuppressant may be expected (CYP3A4 induction). These immunosuppressants are not anticipated to affect exposure of efavirenz.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>OPIOIDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone/Efavirenz (stable maintenance, 35-100 mg once daily/600 mg once daily)</td>
<td>Methadone: AUC: ↓ 52% (↓ 33 to ↓ 66) C&lt;sub&gt;max&lt;/sub&gt;: ↓ 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.</td>
<td>Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.</td>
</tr>
<tr>
<td>Buprenorphine/naloxone/Efavirenz</td>
<td>Buprenorphine: AUC: ↓ 50% Norbuprenorphine: AUC: ↓ 71% Efavirenz: No clinically significant pharmacokinetic interaction</td>
<td>Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine or efavirenz may not be necessary when co-administered.</td>
</tr>
</tbody>
</table>

<sup>90% confidence intervals unless otherwise noted.<sup>a 95% confidence intervals.</sup>

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Efavirenz should not be used during pregnancy unless there are no other appropriate treatment options.

*Women of childbearing potential*: pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.

*Pregnancy*: there are limited amount of data from the use of efavirenz in pregnant women. In postmarketing experience through an antiretroviral pregnancy registry, outcomes for more than 400 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been prospectively reported with no specific malformation pattern observed. A small number of cases of neural tube defects, including meningomyelocele, have been reported via the registry. Most neural tube defects were isolated retrospectively reported cases, and causality cannot be
ruled out but has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects (see section 5.3).

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

**a. Summary of the safety profile**

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported adverse reactions of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most notable adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2 - 4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; psychiatric adverse reactions including severe depression, death by suicide, and psychosis like behaviour; and seizures have been reported in patients treated with efavirenz. The administration of SUSTIVA with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

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

**b. Tabulated list of adverse reactions**

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below. Also listed in italics are adverse reactions observed post-marketing in association with efavirenz-containing antiretroviral treatment regimens. Frequency is defined using the following convention: very common (≥ 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).

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>common</td>
<td>abnormal dreams, anxiety, depression, insomnia*</td>
</tr>
<tr>
<td>uncommon</td>
<td>affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis†, suicide attempt, suicide ideation*</td>
</tr>
<tr>
<td>rare</td>
<td>delusion†, neurosis‡, completed suicide‡*</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>common</td>
<td>cerebellar coordination and balance disturbances†, disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%)*</td>
</tr>
<tr>
<td>uncommon</td>
<td>agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal, *tremor†</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>vision blurred</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>tinnitus†, vertigo</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>flushing†</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>common</td>
<td>abdominal pain, diarrhoea, nausea, vomiting</td>
</tr>
<tr>
<td>uncommon</td>
<td>pancreatitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>hepatitis acute</td>
</tr>
<tr>
<td>rare</td>
<td>hepatic failure‡*</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>very common</td>
<td>rash (11.6%)*</td>
</tr>
<tr>
<td>common</td>
<td>pruritus</td>
</tr>
<tr>
<td>uncommon</td>
<td>erythema multiforme, Stevens-Johnson syndrome*</td>
</tr>
<tr>
<td>rare</td>
<td>photoallergic dermatitis‡</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
</tr>
<tr>
<td>uncommon</td>
<td>gynaecomastia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>common</td>
<td>fatigue</td>
</tr>
</tbody>
</table>

*See section c. Description of selected adverse reactions for more details.
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).

c. Description of selected adverse reactions

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:

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz regimen (n=1,008)</th>
<th>Control regimen (n=635)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- severe depression</td>
<td>1.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>- suicidal ideation</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- non-fatal suicide attempts</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>- aggressive behaviour</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- paranoid reactions</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>- manic reactions</td>
<td>0.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

Nervous system symptoms: in clinical controlled trials, frequently reported adverse reactions included, but were not limited to dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms of moderate-to-severe intensity were experienced by 19.4% (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 (see section 4.4).

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

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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

**Laboratory test abnormalities:**

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

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

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

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

d. Paediatric population

Undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (in a clinical study including 57 children who received efavirenz during a 48-week period, rash was reported in 46%) and was more often of higher grade than in adults (severe rash was reported in 5.3% of children). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered. Although nervous system symptoms are difficult for young children to report, they appear to be less frequent in children and were generally mild. In the study of 57 children, 3.5% of patients experienced nervous system symptoms of moderate intensity, predominantly dizziness. No child had severe symptoms or had to discontinue because of nervous system symptoms. Diarrhoea occurred in six of nineteen (32%) children, aged 3 - 8 years, who took efavirenz oral solution in combination with nelfinavir (20 - 30 mg/kg given three times a day) and one or more NRTIs.

e. Other special populations

Liver enzymes in hepatitis B or C co-infected patients: in the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among co-infected patients in study 006, elevations in AST to greater than five times ULN developed in 13% of efavirenz-treated patients and in 7% of controls, and elevations in ALT to greater than five times ULN developed in 20% s 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).

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: 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).

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 medications used in combination with efavirenz.

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

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

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

Clinical efficacy:

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

Two controlled studies (006 and ACTG 364) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naive 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/mm³ and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 4. In the analysis of responder rates (the non-completer equals failure analysis [NC = F]), patients who terminated the study early for any reason, or who had a missing HIV-RNA measurement that was
either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 50 or above 400 copies/ml at the missing time points.

### Table 4: Efficacy results for study 006

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>n</th>
<th>48 weeks</th>
<th>48 weeks</th>
<th>48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV + ZDV + 3TC</td>
<td>202</td>
<td>67%</td>
<td>62%</td>
<td>187</td>
</tr>
<tr>
<td>EFV + IDV</td>
<td>206</td>
<td>54%</td>
<td>48%</td>
<td>177</td>
</tr>
<tr>
<td>IDV + ZDV + 3TC</td>
<td>206</td>
<td>45%</td>
<td>40%</td>
<td>153</td>
</tr>
</tbody>
</table>

- **Plasma HIV-RNA Mean change from baseline-CD4 cell count (95% C.I.)**

  - < 400 copies/ml (95% C.I.):
    - EFV + ZDV + 3TC: 62%
    - EFV + IDV: 48%
    - IDV + ZDV + 3TC: 40%
  - < 50 copies/ml (95% C.I.):
    - EFV + ZDV + 3TC: 55%, 69%
    - EFV + IDV: 41%, 55%
    - IDV + ZDV + 3TC: 34%, 47%

### Notes:
- **NC = F**, noncompleter = failure.
- **C.I.**, confidence interval.
- **S.E.M.**, standard error of the mean.
- **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 5. 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 5: Efficacy results for studies ACTG 364 and 020

<table>
<thead>
<tr>
<th>Study Number/ Treatment Regimens</th>
<th>n</th>
<th>% (95% C.I. c)</th>
<th>% (95% C.I.)</th>
<th>Mean change from baseline-CD4 cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ACTG 364</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV + NFV + NRTIs</td>
<td>65</td>
<td>70 (59, 82)</td>
<td>---</td>
<td>107 (17.9)</td>
</tr>
<tr>
<td>EFV + NRTIs</td>
<td>65</td>
<td>58 (46, 70)</td>
<td>---</td>
<td>114 (21.0)</td>
</tr>
<tr>
<td>NFV + NRTIs</td>
<td>66</td>
<td>30 (19, 42)</td>
<td>---</td>
<td>94 (13.6)</td>
</tr>
<tr>
<td>Study 020</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV + IDV + NRTIs</td>
<td>157</td>
<td>60 (52, 68)</td>
<td>49 (41, 58)</td>
<td>104 (9.1)</td>
</tr>
<tr>
<td>IDV + NRTIs</td>
<td>170</td>
<td>51 (43, 59)</td>
<td>38 (30, 45)</td>
<td>77 (9.9)</td>
</tr>
</tbody>
</table>

---, not performed.

NC = F, noncompleter = failure.

EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir.

C.I., confidence interval for proportion of patients in response.

S.E.M., standard error of the mean.

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

5.2 Pharmacokinetic properties

Absorption: peak efavirenz plasma concentrations of 1.6 - 9.1 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 Cₘₚₙ 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 Cₘₚₙ, mean Cₖᵢₙ, 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 Cₘₚₙ was 12.9 ± 3.7 μM (29%) [mean ± S.D. (% C.V.)], steady state Cₖᵢₙ was 5.6 ± 3.2 μM (57%), and AUC was 184 ± 73 μM·h (40%).

In uninfected adult volunteers, the Cₘₚₙ and AUC of a 240 mg dose of SUSTIVA oral solution were 78% and 97%, respectively, of the values measured when SUSTIVA was given as a 200 mg hard capsule.

Effect of food: the AUC and Cₘₚₙ of a single 240 mg dose of efavirenz oral solution in uninfected adult volunteers was increased by 30% and 43%, respectively, when given with a high-fat meal, relative to fasted conditions.
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 P450 enzymes, resulting in the induction of its own metabolism. 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).

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 pharmacokinetics
The equivalent of a 600 mg dose of efavirenz was given as hard capsules (dose adjusted from calculated body size based on weight) to 49 paediatric patients. The pharmacokinetics of efavirenz in paediatric patients were similar to adults. Steady state C\textsubscript{max} was 14.1 \(\mu\)M, steady state C\textsubscript{min} was 5.6 \(\mu\)M, and AUC was 216 \(\mu\)M·h. In 17 paediatric patients receiving an investigational oral solution similar to the commercial formulation adjusted on the basis of body size to be equivalent to an adult 600 mg capsule dose, the steady-state C\textsubscript{max} was 11.8 \(\mu\)M, steady state C\textsubscript{min} was 5.2 \(\mu\)M, and AUC was 188 \(\mu\)M·h. In the subset of 6 children aged 3 - 5 who were compliant with their drug regimen, the mean AUC was 147 \(\mu\)M·h, which was 23% lower than expected. Therefore, the dosage recommendation provided in Table 1 incorporates a higher dose of efavirenz oral solution for these younger children.
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 $\geq 1$ 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 $\geq 1$ 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

Medium chain triglycerides
Benzoic acid (E210)
Strawberry/mint flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening: 1 month.

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 containing 180 ml of oral solution. Each carton contains 1 bottle. An oral syringe with a push-in bottle-neck adapter is included in the carton.

6.6 Special precautions for disposal

No special requirements.
7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/005 - bottle

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 May 1999
Date of latest renewal: 28 May 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site:
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: each film-coated tablet contains 249.6 mg of lactose monohydrate.

For a 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 years of age and older.

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

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

4.2 Posology and method of administration

Posology

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

*Concomitant antiretroviral therapy:* SUSTIVA must be given in combination with other antiretroviral medicines (see section 4.5).

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

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

*Adults and adolescents over 40 kg:* the recommended dose of SUSTIVA 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 SUSTIVA is coadministered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the SUSTIVA 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 SUSTIVA is coadministered with rifampicin, an increase in the dose of SUSTIVA 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).

### 4.3 Contraindications

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

Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Class C) (see section 5.2).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects [for example, cardiac arrhythmias, prolonged sedation or respiratory depression] (see section 4.5).

Herbal preparations containing St. John's wort (*Hypericum perforatum*) must not be used while taking efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

### 4.4 Special warnings and precautions for use

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance (see section 5.1).

Co-administration of efavirenz with the fixed combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate is not recommended.

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

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

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

Rash: mild-to-moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus (see section 4.8).

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

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

Nervous system symptoms: symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Seizures: convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

Hepatic events: a few of the 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.

Effect of food: the administration of SUSTIVA 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 SUSTIVA 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.

Lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Osteonecrosis: although the etiology 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 years of age or who weigh less than 13 kg. Therefore, efavirenz should not be given to children less than 3 years of age.
Rash was reported in 26 of 57 children (46%) treated with efavirenz during a 48-week period and was severe in three patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

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

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4 (see section 5.2). Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.

Contraindications of concomitant use

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozone, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

St. John’s wort (Hypericum perforatum): co-administration of efavirenz and St. John’s wort or herbal preparations containing St. John’s wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John’s wort due to induction of drug metabolising enzymes and/or transport proteins by St. John’s wort. If a patient is already taking St. John’s wort, stop St. John’s wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John’s wort and the dose of efavirenz may need adjusting. The inducing effect of St. John’s wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

Other interactions

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

Table 1: Interactions between efavirenz and other medicinal products

<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td><strong>Mean percent change in AUC, C_{max}, C_{min} with confidence intervals if available</strong></td>
<td><strong>Recommendation concerning co-administration with efavirenz</strong></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td><strong>(mechanism)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Protease inhibitors (PI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/ritonavir/efavirenz (400 mg once daily/100 mg once daily/600 mg once daily, all administered with food)</td>
<td>Atazanavir (pm): AUC: ↔* (↓9 to ↑10) C_{max}: ↑17%* (↑8 to ↑27) C_{min}: ↓42%* (↓31 to ↓51)</td>
<td>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</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels: Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Atazanavir/ritonavir/EFavirenz (400 mg once daily/200 mg once daily, all administered with food)</td>
<td>Atazanavir (pm):</td>
<td>* Atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close clinical monitoring.</td>
</tr>
<tr>
<td></td>
<td>AUC: ↔-** (↓10 to ↑26)</td>
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<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: ↔*/** (↓5 to ↑26)</td>
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<tr>
<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt;: ↑12%*/** (↑16 to ↓49) (CYP3A4 induction).</td>
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<tr>
<td></td>
<td>* When compared to atazanavir 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C&lt;sub&gt;min&lt;/sub&gt; might negatively impact the efficacy of atazanavir.</td>
<td></td>
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<tr>
<td></td>
<td>** based on historical comparison</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir/EFavirenz (300 mg twice daily*/100 mg twice daily/600 mg once daily)</td>
<td>Darunavir:</td>
<td>The clinical significance of the changes has not been established. Similar findings are expected with the approved darunavir/ritonavir 600/100 mg twice daily dose. This combination should be used with caution. See ritonavir row below.</td>
</tr>
<tr>
<td></td>
<td>AUC: ↓13%</td>
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<tr>
<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt;: ↓31%</td>
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<tr>
<td></td>
<td>(CYP3A4 induction)</td>
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<tr>
<td></td>
<td>Efavirenz:</td>
<td></td>
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<tr>
<td></td>
<td>AUC: ↑21%</td>
<td></td>
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<tr>
<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt;: ↑17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CYP3A4 inhibition)</td>
<td></td>
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<tr>
<td></td>
<td>*lower than recommended dose</td>
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</tr>
<tr>
<td>Fosamprenavir/ritonavir/EFavirenz (700 mg twice daily/100 mg twice daily/600 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction</td>
<td>No dose adjustment is necessary for any of these medicinal products. See also ritonavir row below.</td>
</tr>
<tr>
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<tr>
<td>Fosamprenavir/Nelfinavir/EFavirenz</td>
<td>Interaction not studied.</td>
<td>No dose adjustment is necessary for any of these medicinal products. Not recommended as the exposure to both PIs is expected to be significantly decreased.</td>
</tr>
<tr>
<td>Fosamprenavir/Saquinavir/EFavirenz</td>
<td>Interaction not studied.</td>
<td></td>
</tr>
<tr>
<td>Indinavir/Efavirenz (800 mg q8h/200 mg once daily)</td>
<td>Indinavir:</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>AUC : ↓31% (↓8 to ↓47)</td>
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<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt; : ↓40%</td>
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<tr>
<td></td>
<td>A similar reduction in indinavir exposures was observed when indinavir 1000 mg q8h was given with efavirenz 600 mg daily. (CYP3A4 induction)</td>
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</tr>
<tr>
<td></td>
<td>Efavirenz:</td>
<td>No dose adjustment is necessary</td>
</tr>
<tr>
<td></td>
<td>No clinically significant pharmacokinetic interaction</td>
<td></td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C_max, C_min with confidence intervals if available (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
</tr>
<tr>
<td>---------------------------------------------</td>
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<td>----------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 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. | for efavirenz when given with indinavir or indinavir/ritonavir.  
See also ritonavir row below. |
| 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. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C\text{max}, C\text{min} with confidence intervals if available\textsuperscript{a} (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| **Ritonavir/Efavirenz** (500 mg twice daily/600 mg once daily) | Ritonavir:  
Morning AUC: ↑ 18% (↑ 6 to ↑ 33)  
Evening AUC: ↔  
Morning C\text{max}: ↑ 24% (↑ 12 to ↑ 38)  
Evening C\text{max}: ↔  
Morning C\text{min}: ↑ 42% (↑ 9 to ↑ 86) \textsuperscript{b}  
Evening C\text{min}: ↑ 24% (↑ 3 to ↑ 50) \textsuperscript{b}  
Efavirenz:  
AUC: ↑ 21% (↑ 10 to ↑ 34)  
C\text{max}: ↑ 14% (↑ 4 to ↑ 26)  
C\text{min}: ↑ 25% (↑ 7 to ↑ 46) \textsuperscript{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\textsubscript{12}: ↓ 45% (↓ 38 to ↓ 51)  
C\text{max}: ↓ 51% (↓ 37 to ↓ 62)  
Efavirenz concentrations not measured, no effect is expected. | Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc. |
| **Integrase strand transfer inhibitor** | **Raltegravir/Efavirenz** (400 mg single dose/-) | Raltegravir:  
AUC: ↓ 36%  
C\text{12}: ↓ 21%  
C\text{max}: ↓ 36% (UGT1A1 induction) | No dose adjustment is necessary for raltegravir. |
<p>| <strong>NRTIs and NNRTIs</strong> | <strong>NRTIs/Efavirenz</strong> | Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine, and tenofovir disoproxil fumarate. Clinically significant interactions are not expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways. | No dose adjustment is necessary for either medicinal product. |
| | <strong>NNRTIs/Efavirenz</strong> | Interaction not studied. | Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of efavirenz |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, $C_{\text{max}}$, $C_{\text{min}}$ with confidence intervals if availablea (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
<td>and another NNRTI is not recommended.</td>
</tr>
<tr>
<td>Azithromycin/Efavirenz (600 mg single dose/400 mg once daily)</td>
<td>No clinically significant pharmacokinetic interaction.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td>Clarithromycin/Efavirenz (500 mg q12h/400 mg once daily)</td>
<td>Clarithromycin: AUC: ↓ 39% (↓ 30 to ↓ 46) $C_{\text{max}}$: ↓ 26% (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34% (↑ 18 to ↑ 53) $C_{\text{max}}$: ↑ 49% (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ $C_{\text{max}}$: ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin.</td>
<td>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.</td>
</tr>
<tr>
<td>Other macrolide antibiotics (e.g., erythromycin)/Efavirenz</td>
<td>Interaction not studied.</td>
<td>No data are available to make a dose recommendation.</td>
</tr>
<tr>
<td>Rifabutin/Efavirenz (300 mg once daily/600 mg once daily)</td>
<td>Rifabutin: AUC: ↓ 38% (↓ 28 to ↓ 47) $C_{\text{max}}$: ↓ 32% (↓ 15 to ↓ 46) $C_{\text{min}}$: ↓ 45% (↓ 31 to ↓ 56) Efavirenz: AUC: ↔ $C_{\text{max}}$: ↔ $C_{\text{min}}$: ↓ 12% (↓ 24 to ↑ 1) (CYP3A4 induction)</td>
<td>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.</td>
</tr>
<tr>
<td>Rifampicin/Efavirenz (600 mg once daily/600 mg once daily)</td>
<td>Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) $C_{\text{max}}$: ↓ 20% (↓ 11 to ↓ 28) $C_{\text{min}}$: ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)</td>
<td>When taken with rifampicin, 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.</td>
</tr>
<tr>
<td>Medicinal product by therapeutic areas (dose)</td>
<td>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</td>
<td>Recommendation concerning co-administration with efavirenz</td>
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<tr>
<td><strong>Antifungals</strong></td>
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</tbody>
</table>
| Itraconazole/Efavirenz (200 mg q12h/600 mg once daily) | Itraconazole:  
AUC: ↓ 39% (↓ 21 to ↓ 53)  
C<sub>max</sub>: ↓ 37% (↓ 20 to ↓ 51)  
C<sub>min</sub>: ↓ 44% (↓ 27 to ↓ 58)  
(decrease in itraconazole concentrations: CYP3A4 induction)  
Hydroxyitraconazole:  
AUC: ↓ 37% (↓ 14 to ↓ 55)  
C<sub>max</sub>: ↓ 35% (↓ 12 to ↓ 52)  
C<sub>min</sub>: ↓ 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. |
| Posaconazole/Efavirenz --/400 mg once daily | Posaconazole:  
AUC: ↓ 50%  
C<sub>max</sub>: ↓ 45%  
(UDP-G induction) | Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk. |
| Voriconazole/Efavirenz (200 mg twice daily/400 mg once daily) | Voriconazole:  
AUC: ↓ 77%  
C<sub>max</sub>: ↓ 61%  
Efavirenz:  
AUC: ↑ 44%  
C<sub>max</sub>: ↑ 38%  
Voriconazole:  
AUC: ↓ 7% (↓ 23 to ↑ 13) *  
C<sub>max</sub>: ↑ 23% (↓ 1 to ↑ 53) *  
Efavirenz:  
AUC: ↑ 17% (↑ 6 to ↑ 29) **  
C<sub>max</sub>: ↔**  
*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. |
| Voriconazole/Efavirenz (400 mg twice daily/300 mg once daily) | | |
| 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. |
| **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<sub>max</sub>: ↑ 16% (↑ 2 to ↑ 32)  
These changes are not considered clinically significant. | No dose adjustment is necessary for either medicinal product. |
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in ( \text{AUC, } C_{\text{max}}, \ C_{\text{min}} ) with confidence intervals if available ( ^a ) (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin/Efavirenz</td>
<td>Interaction not studied. Plasma concentrations and effects of warfarin are potentially increased or decreased by efavirenz.</td>
<td>Dose adjustment of warfarin may be required.</td>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Carbamazepine/Efavirenz (400 mg once daily/600 mg once daily) | Carbamazepine:  
\( \text{AUC: } \downarrow 27\% (\downarrow 20 \text{ to } \downarrow 33) \)  
\( \text{C}_{\text{max}}: \downarrow 20\% (\downarrow 15 \text{ to } \downarrow 24) \)  
\( \text{C}_{\text{min}}: \downarrow 35\% (\downarrow 24 \text{ to } \downarrow 44) \)  
Efavirenz:  
\( \text{AUC: } \downarrow 36\% (\downarrow 32 \text{ to } \downarrow 40) \)  
\( \text{C}_{\text{max}}: \downarrow 21\% (\downarrow 15 \text{ to } \downarrow 26) \)  
\( \text{C}_{\text{min}}: \downarrow 47\% (\downarrow 41 \text{ to } \downarrow 53) \)  
(decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction)  
The steady-state \( \text{AUC, C}_{\text{max}} \) and \( \text{C}_{\text{min}} \) of the active carbamazepine epoxide metabolite remained unchanged.  
Co-administration of higher doses of either efavirenz or carbamazepine has not been studied. | No 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. |
| 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:  
\( \text{AUC: } \downarrow 39\% (\downarrow 27 \text{ to } \downarrow 50) \)  
\( \text{C}_{\text{max}}: \downarrow 29\% (\downarrow 15 \text{ to } \downarrow 40) \)  
\( \text{C}_{\text{min}}: \downarrow 46\% (\downarrow 31 \text{ to } \downarrow 58) \)  
Efavirenz:  
\( \text{AUC: } \leftrightarrow \)  
\( \text{C}_{\text{max}}: \uparrow 11\% (\uparrow 6 \text{ to } \uparrow 16) \)  
\( \text{C}_{\text{min}}: \leftrightarrow \)  
(CYP3A4 induction) | Sertraline dose increases should be guided by clinical response.  
No dose adjustment is necessary for efavirenz. |
<p>| Paroxetine/Efavirenz (20 mg once daily/600 mg once daily) | No clinically significant pharmacokinetic interaction | No dose adjustment is necessary for either medicinal product. |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, $C_{\text{max}}$, $C_{\text{min}}$ with confidence intervals if available$^a$ (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine/Efavirenz</td>
<td>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.</td>
<td>No dose adjustment is necessary for either medicinal product.</td>
</tr>
<tr>
<td><strong>ANTIHISTAMINES</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Cetirizine/Efavirenz (10 mg single dose/600 mg once daily) | Cetirizine:  
AUC: ↔  
$C_{\text{max}}$: ↓ 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. |
| **CARDIOVASCULAR AGENTS**                   |                                                                                             |                                                  |
| **Calcium Channel Blockers**                |                                                                                             |                                                  |
| Diltiazem/Efavirenz (240 mg once daily/600 mg once daily) | Diltiazem:  
AUC: ↓ 69% (↓ 55 to ↓ 79)  
$C_{\text{max}}$: ↓ 60% (↓ 50 to ↓ 68)  
$C_{\text{min}}$: ↓ 63% (↓ 44 to ↓ 75)  
Desacetyl diltiazem:  
AUC: ↓ 75% (↓ 59 to ↓ 84)  
$C_{\text{max}}$: ↓ 64% (↓ 57 to ↓ 69)  
$C_{\text{min}}$: ↓ 62% (↓ 44 to ↓ 75)  
N-monodesmethyl diltiazem:  
AUC: ↓ 37% (↓ 17 to ↓ 52)  
$C_{\text{max}}$: ↓ 28% (↓ 7 to ↓ 44)  
$C_{\text{min}}$: ↓ 37% (↓ 17 to ↓ 52)  
Efavirenz:  
AUC: ↑ 11% (↑ 5 to ↑ 18)  
$C_{\text{max}}$: ↑ 16% (↑ 6 to ↑ 26)  
$C_{\text{min}}$: ↑ 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. |
<p>| 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). |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, $C_{\text{max}}$, $C_{\text{min}}$ with confidence intervals if available(^a) (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG Co-A Reductase Inhibitors</strong></td>
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</tr>
</tbody>
</table>
| **Atorvastatin/Efavirenz (10 mg once daily/600 mg once daily)** | Atorvastatin:  
AUC: ↓ 43% (↓ 34 to ↓ 50)  
$C_{\text{max}}$: ↓ 12% (↓ 1 to ↓ 26)  
2-hydroxy atorvastatin:  
AUC: ↓ 35% (↓ 13 to ↓ 40)  
$C_{\text{max}}$: ↓ 13% (↓ 0 to ↓ 23)  
4-hydroxy atorvastatin:  
AUC: ↓ 4% (↓ 0 to ↓ 31)  
$C_{\text{max}}$: ↓ 47% (↓ 9 to ↓ 51)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 34% (↓ 21 to ↓ 41)  
$C_{\text{max}}$: ↓ 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)  
$C_{\text{max}}$: ↓ 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. |
| **Simvastatin/Efavirenz (40 mg once daily/600 mg once daily)** | Simvastatin:  
AUC: ↓ 69% (↓ 62 to ↓ 73)  
$C_{\text{max}}$: ↓ 76% (↓ 63 to ↓ 79)  
Simvastatin acid:  
AUC: ↓ 58% (↓ 39 to ↓ 68)  
$C_{\text{max}}$: ↓ 51% (↓ 32 to ↓ 58)  
Total active HMG Co-A reductase inhibitors:  
AUC: ↓ 60% (↓ 52 to ↓ 68)  
$C_{\text{max}}$: ↓ 62% (↓ 55 to ↓ 78)  
(CYP3A4 induction)  
Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or $C_{\text{max}}$ 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. |
<p>| <strong>Rosuvastatin/Efavirenz</strong> | 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. |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HORMONAL CONTRACEPTIVES</strong></td>
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</tbody>
</table>
| Oral: Ethinyloestradiol + Norgestimate/ Efavirenz (0.035 mg + 0.25 mg once daily/600 mg once daily) | Ethinyloestradiol:  
AUC: ↔  
C<sub>max</sub>: ↔  
C<sub>min</sub>: ↓ 8% (↑ 14 to ↓ 25)  
Norelgestromin (active metabolite):  
AUC: ↓ 64% (↓ 62 to ↓ 67)  
C<sub>max</sub>: ↓ 46% (↓ 39 to ↓ 52)  
C<sub>min</sub>: ↓ 82% (↓ 79 to ↓ 85)  
Levonorgestrel (active metabolite):  
AUC: ↓ 83% (↓ 79 to ↓ 87)  
C<sub>max</sub>: ↓ 80% (↓ 77 to ↓ 83)  
C<sub>min</sub>: ↓ 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). |
<p>| 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 Interaction not studied. 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). |
| <strong>IMMUNOSUPPRESSANTS</strong>                      |                                                                                                               |                                                             |
| 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. |
| <strong>OPIOIDS</strong>                                 |                                                                                                               |                                                             |</p>
<table>
<thead>
<tr>
<th>Medicinal product by therapeutic areas (dose)</th>
<th>Effects on drug levels Mean percent change in AUC, C&lt;sub&gt;max&lt;/sub&gt;, C&lt;sub&gt;min&lt;/sub&gt; with confidence intervals if available&lt;sup&gt;a&lt;/sup&gt; (mechanism)</th>
<th>Recommendation concerning co-administration with efavirenz</th>
</tr>
</thead>
</table>
| Methadone/Efavirenz (stable maintenance, 35-100 mg once daily/600 mg once daily) | Methadone:  
AUC: ↓ 52% (↓ 33 to ↓ 66)  
C<sub>max</sub>: ↓ 45% (↓ 25 to ↓ 59)  
(CYP3A4 induction)  
In a study of HIV infected intravenous drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. | Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms. |
| Buprenorphine/naloxone/Efavirenz | Buprenorphine:  
AUC: ↓ 50%  
Norbuprenorphine:  
AUC: ↓ 71%  
Efavirenz:  
No clinically significant pharmacokinetic interaction | Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine or efavirenz may not be necessary when co-administered. |

<sup>a</sup> 90% confidence intervals unless otherwise noted.  
<sup>b</sup> 95% confidence intervals.

**Paediatric population**

Interaction studies have only been performed in adults.

### 4.6 Fertility, pregnancy and lactation

Efavirenz should not be used during pregnancy unless there are no other appropriate treatment options.

**Women of childbearing potential:** pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.

**Pregnancy:** there are limited amount of data from the use of efavirenz in pregnant women. In postmarketing experience through an antiretroviral pregnancy registry, outcomes for more than 400 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been prospectively reported with no specific malformation pattern observed. A small number of cases of neural tube defects, including meningomyelocele, have been reported via the registry. Most neural tube defects were isolated retrospectively reported cases, and causality cannot be ruled out but has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects (see section 5.3).

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported adverse reactions of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most notable adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2 - 4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; psychiatric adverse reactions including severe depression, death by suicide, and psychosis like behaviour; and seizures have been reported in patients treated with efavirenz. The administration of SUSTIVA with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

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

b. Tabulated list of adverse reactions

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below. Also listed in italics are adverse reactions observed post-marketing in association with efavirenz-containing antiretroviral treatment regimens. Frequency is defined using the following convention: very common (≥ 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); or not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td>hypersensitivity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td>abnormal dreams, anxiety, depression, insomnia*</td>
</tr>
<tr>
<td>uncommon</td>
<td>affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis*, suicide attempt, suicide ideation*</td>
</tr>
<tr>
<td>rare</td>
<td>delusion*, neurosis*, completed suicide*</td>
</tr>
</tbody>
</table>

122
<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td><em>cerebellar coordination and balance disturbances†</em>, disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%)*</td>
</tr>
<tr>
<td>uncommon</td>
<td>agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal,* tremor†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td>vision blurred</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ear and labyrinth disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td><em>tinnitus†</em>, vertigo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td><em>flushing†</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td>abdominal pain, diarrhoea, nausea, vomiting</td>
</tr>
<tr>
<td>uncommon</td>
<td>pancreatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td>hepatitis acute</td>
</tr>
<tr>
<td>rare</td>
<td><em>hepatic failure‡</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>rush (11.6%)*</td>
</tr>
<tr>
<td>common</td>
<td>pruritus</td>
</tr>
<tr>
<td>uncommon</td>
<td><em>erythema multiforme, Stevens-Johnson syndrome</em></td>
</tr>
<tr>
<td>rare</td>
<td><em>photoallergic dermatitis†</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproductive system and breast disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>uncommon</td>
<td>gynaecomastia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td>fatigue</td>
</tr>
<tr>
<td>common</td>
<td>fatigue</td>
</tr>
</tbody>
</table>

*See section c. Description of selected adverse reactions for more details.
†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).
c. Description of selected adverse reactions

*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:

<table>
<thead>
<tr>
<th>Efavirenz regimen (n=1,008)</th>
<th>Control regimen (n=635)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- severe depression</td>
<td>1.6%</td>
</tr>
<tr>
<td>- suicidal ideation</td>
<td>0.6%</td>
</tr>
<tr>
<td>- non-fatal suicide attempts</td>
<td>0.4%</td>
</tr>
<tr>
<td>- aggressive behaviour</td>
<td>0.4%</td>
</tr>
<tr>
<td>- paranoid reactions</td>
<td>0.4%</td>
</tr>
<tr>
<td>- manic reactions</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

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

*Nervous system symptoms:* in clinical controlled trials, frequently reported adverse reactions included, but were not limited to dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms of moderate-to-severe intensity were experienced by 19% (severe 2%) of patients compared to 9% (severe 1%) of patients receiving control regimens. In clinical studies 2% of patients treated with efavirenz discontinued therapy due to such symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Nervous system symptoms may occur more frequently when efavirenz is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms and can be recommended during the first weeks of therapy and in patients who continue to experience these symptoms (see section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit.

Analysis of long-term data showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the control arm.
**Hepatic failure:** A few of the 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 (see section 4.4).

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

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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

**Laboratory test abnormalities:**

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

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

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

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

**d. Paediatric population**

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

**e. Other special populations**

*Liver enzymes in hepatitis B or C co-infected patients:* in the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among co-infected patients in study 006, elevations in AST to greater than five times ULN developed in 13% of efavirenz-treated patients and in 7% of control, and elevations in ALT to greater than five times ULN developed in 20% and 7%, respectively. Among co-infected patients, 3% of those treated with efavirenz and 2% in the control arm discontinued because of liver disorders (see section 4.4).

**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: 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).

*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 medications used in combination with efavirenz.

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

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

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

Clinical efficacy:

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

Two controlled studies (006 and ACTG 364) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naïve and NRTI-experienced HIV-infected patients. Study 020 showed similar activity in NRTI-experienced patients over 24 weeks. In these studies the dose of efavirenz was 600 mg once daily; the dose of indinavir was 1,000 mg every 8 hours when used with efavirenz and 800 mg every 8 hours when used without efavirenz. The dose of nelfinavir was 750 mg given three times a day. The standard doses of NRTIs given every 12 hours were used in each of these studies.

Study 006, a randomized, open-label trial, compared efavirenz + zidovudine + lamivudine or efavirenz + indinavir with indinavir + zidovudine + lamivudine in 1,266 patients who were required to be efavirenz-, lamivudine-, NNRTI-, and PI-naïve at study entry. The mean baseline CD4 cell count was 341 cells/mm³ and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 2. In the analysis of responder rates (the non-completer equals failure analysis [NC = F]), patients who terminated the study early for any reason, or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 50 or above 400 copies/ml at the missing time points.
Table 2: Efficacy results for study 006

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>n</th>
<th>48 weeks</th>
<th>48 weeks</th>
<th>48 weeks</th>
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</thead>
<tbody>
<tr>
<td>EFV + ZDV + 3TC</td>
<td>202</td>
<td>67%</td>
<td>62%</td>
<td>187</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(60%, 73%)</td>
<td>(55%, 69%)</td>
<td>(11.8)</td>
</tr>
<tr>
<td>EFV + IDV</td>
<td>206</td>
<td>54%</td>
<td>48%</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(47%, 61%)</td>
<td>(41%, 55%)</td>
<td>(11.3)</td>
</tr>
<tr>
<td>IDV + ZDV + 3TC</td>
<td>206</td>
<td>45%</td>
<td>40%</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(38%, 52%)</td>
<td>(34%, 47%)</td>
<td>(12.3)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Number/Treatment Regimens</th>
<th>n</th>
<th>% (95% C.I.)</th>
<th>% (95% C.I.)</th>
<th>Mean change from baseline-CD4 cell count (S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ACTG 364</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV + NFV + NRTIs</td>
<td>65</td>
<td>70 (59, 82)</td>
<td>---</td>
<td>107 (17.9)</td>
</tr>
<tr>
<td>EFV + NRTIs</td>
<td>65</td>
<td>58 (46, 70)</td>
<td>---</td>
<td>114 (21.0)</td>
</tr>
<tr>
<td>NFV + NRTIs</td>
<td>66</td>
<td>30 (19, 42)</td>
<td>---</td>
<td>94 (13.6)</td>
</tr>
<tr>
<td>Study 020</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV + IDV + NRTIs</td>
<td>157</td>
<td>60 (52, 68)</td>
<td>49 (41, 58)</td>
<td>104 (9.1)</td>
</tr>
<tr>
<td>IDV + NRTIs</td>
<td>170</td>
<td>51 (43, 59)</td>
<td>38 (30, 45)</td>
<td>77 (9.9)</td>
</tr>
</tbody>
</table>

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 interval for proportion of patients in response.
---, not performed.
Paediatric population: ACTG 382 is an ongoing uncontrolled study of 57 NRTI-experienced paediatric patients (3 - 16 years) which characterises the pharmacokinetics, antiviral activity and safety of efavirenz in combination with nelfinavir (20 - 30 mg/kg given three times a day) and one or more NRTIs. The starting dose of efavirenz was the equivalent of a 600 mg dose (adjusted from calculated body size based on weight). The response rate, based on the NC = F analysis of the percentage of patients with plasma HIV-RNA < 400 copies/ml at 48 weeks was 60% (95%, C.I. 47, 72), and 53% (C.I. 40, 66) based on percentage of patients with plasma HIV-RNA < 50 copies/ml. The mean CD4 cell counts were increased by 63 ± 34.5 cells/mm³ from baseline. The durability of the response was similar to that seen in adult patients.

5.2 Pharmacokinetic properties

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

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

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

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

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

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

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. 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).

Elimination: efavirenz has a relatively long terminal half-life of at least 52 hours after single doses and 40 - 55 hours after multiple doses. Approximately 14 - 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.
**Hepatic impairment:** In a single-dose study, half life was doubled in the single patient with severe hepatic impairment (Child Pugh Class C), indicating a potential for a much greater degree of accumulation. A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics.

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

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

### 5.3 Preclinical safety data
Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays.

Efavirenz induced foetal resorptions in rats. Malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, microphthalmia 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 $\geq$ 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 $\geq$ 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**
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 90 (3 x 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
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

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: 28 May 2009
10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site:
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb
Champ “Lachaud”
La Goualle
19250 Meymac
France

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

Lawrence Laboratories
Unit 12 Distribution Centre, Shannon Free Zone, Shannon Industrial Estate, Co. Clare
Ireland

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 OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

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

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

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 3.5 presented in Module 1.8.1 of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

PSUR: The Marketing Authorisation Holder will continue to submit annual PSURs.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in version 1.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).
In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached,
- At the request of the EMEA.
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

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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  
Uxbridge Business Park, Sanderson Road  
Uxbridge UB8 1DH  
United Kingdom

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**
**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**

   Oral use.
   Read the package leaflet before use.

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

   Keep out of the reach and sight of children.

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

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
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

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
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

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

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
<table>
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<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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</thead>
<tbody>
<tr>
<td>BLISTER TEXT</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>SUSTIVA 200 mg hard capsules efavirenz</td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
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<td>Bristol-Myers Squibb Pharma EEIG</td>
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<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
### 1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 30 mg/ml oral solution
efavirenz

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains: efavirenz 30 mg

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

180 ml oral solution

### 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP
Use the oral solution within one month after first opening the bottle.

### 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
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/110/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUSTIVA 30 mg/ml
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
90 (3 x 30 x 1) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

Bottle:
EU/1/99/110/008

Blister:
EU/1/99/110/009: 30 x 1 film-coated tablets
EU/1/99/110/010: 90 (3 x 30 x 1) film-coated tablets

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
PARTICULARS TO APPEAR ON THE INTERMEDIATE OUTER PACKAGING

INTERMEDIATE CARTON TEXT FOR BLISTER PACK (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

Blister:
30 x 1 film-coated tablets
Component of a multipack comprising 3 boxes each containing 30 x 1 film-coated tablets. Not to 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

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
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTER TEXT</strong></td>
</tr>
</tbody>
</table>

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
SUSTIVA 50 mg hard capsules

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What SUSTIVA is and what it is used for
2. Before you take SUSTIVA
3. How to take SUSTIVA
4. Possible side effects
5. How to store SUSTIVA
6. Further information

1. WHAT SUSTIVA IS AND WHAT IT IS USED FOR

SUSTIVA 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) infection by reducing the amount of the virus in blood.

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.

2. BEFORE YOU TAKE SUSTIVA

Do not take SUSTIVA
- if you are allergic (hypersensitive) to efavirenz or any of the other ingredients of SUSTIVA listed at the end of this leaflet. Contact your doctor or pharmacist for advice.
- if you have severe liver disease.
- if you are currently taking any of the following medicines:
  - astemizole or terfenadine (used to treat allergy symptoms)
  - bepridil (used to treat heart disease)
  - cisapride (used to treat heartburn)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraine and cluster headaches)
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety)

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.

Take special care with 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, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer. 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).

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.

- changes in body fat. Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Tell your doctor if you notice changes in your body fat.

- bone problems. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint
stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Use in children
SUSTIVA 50 mg hard capsules can be taken by children and adolescents 3 years of age and older and weighing at least 13 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 and cannot tolerate the oral solution (see How to take SUSTIVA).

Taking other medicines
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.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal remedies.

SUSTIVA may interact with other medicines. 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 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

- **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 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 need to change your dose of methadone.
Sertraline (a medicine used to treat depression): your doctor may need to change your dose of sertraline.

Diltiazem or similar medicines (called calcium channel blockers): 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 and breast-feeding). 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 (a medicine used to reduce clotting of the blood): your doctor may need to adjust your dose of warfarin.

Taking SUSTIVA with food and drink
Taking SUSTIVA on an empty stomach may reduce the undesirable effects.

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 during pregnancy. If you have taken SUSTIVA 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 may cause dizziness, impaired concentration, and drowsiness. If you are affected, do not drive and do not use any tools or machines.

Important information about some of the ingredients of SUSTIVA
This medicinal product contains 342 mg of 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. Individuals with these conditions may take SUSTIVA oral solution, which is free from lactose.
3. HOW TO TAKE SUSTIVA

Always take SUSTIVA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- 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.
- 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 Taking other medicines).

Your doctor will give you instructions for proper dosing.

- 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

- The dose for children weighing 40 kg or more is 600 mg once daily.
- The dose for children weighing less than 40 kg is calculated by body weight and is taken once daily as shown below:

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to &lt; 15</td>
<td>200</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>250</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>300</td>
</tr>
<tr>
<td>25 to &lt; 32.5</td>
<td>350</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>400</td>
</tr>
</tbody>
</table>

SUSTIVA oral solution is preferred for children who are not able to swallow the capsules. However, if a child does not tolerate the oral solution, the doctor may recommend opening the hard capsule and mixing the contents with a small amount (1-2 teaspoons) of food (e.g., applesauce, grape jelly, yogurt or infant formula). In a taste preference study, efavirenz mixed with grape jelly received the highest rating. The capsules must be opened carefully so that the contents do not spill or escape into the air. Hold the capsule vertically 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 and do not tolerate the oral solution.

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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, SUSTIVA 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.

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.

The frequency of the side effects listed below is defined using the following conventions:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>affects more than 1 user in 10</td>
</tr>
<tr>
<td>Common</td>
<td>affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>Uncommon</td>
<td>affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>Rare</td>
<td>affects 1 to 10 users in 10,000</td>
</tr>
</tbody>
</table>

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

**Very common side effects**
- skin rash

**Common side effects**
- abnormal dreams, difficulty concentrating, dizziness, headache, difficulty sleeping, drowsiness, problems with coordination or balance
- stomach pain, diarrhoea, feeling sick (nausea), vomiting
- itching
- tiredness
- feeling worried, feeling depressed

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

**Rare**
- 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.

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

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

**If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

5. **HOW TO STORE SUSTIVA**

Keep out of the reach and sight of children.

Do not use SUSTIVA 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What 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.
Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

Manufacturer
Bristol-Myers Squibb
Champ "Lachaud", La Goualle
F- 19250 Meymac
France

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

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

Belgique/België/Belgien
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tél/Tel: +32 (0) 800 38693
MSDBelgium_info@merck.com

Magyarország
MSD Magyarország Kft.
Tel.: +361 888 53 00
hungary_msd@merck.com

Česká republika
Merck Sharp & Dohme IDEA, Inc., org. sl.
Tel.: +420 233 010 111
msd_cr@merck.com

Danmark
Merck Sharp & Dohme
Tlf: +45 43 28 77 66
dkmail@merck.com

Deutschland
Bristol-Myers Squibb GmbH & Co. KGaA
Tel: +49 89 121 42-0

Luxembourg/Luxemburg
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tél/Tel: +32 (0) 800 38693
MSDBelgium_info@merck.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: +357 22866700
malta_info@merck.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800-9999000
medicalinfo.nl@merck.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
msdnorge@msd.no
This leaflet was last approved in
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.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What SUSTIVA is and what it is used for
2. Before you take SUSTIVA
3. How to take SUSTIVA
4. Possible side effects
5. How to store SUSTIVA
6. Further information

1. WHAT SUSTIVA IS AND WHAT IT IS USED FOR

SUSTIVA 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) infection by reducing the amount of the virus in blood.

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.

2. BEFORE YOU TAKE SUSTIVA

Do not take SUSTIVA

- if you are allergic (hypersensitive) to efavirenz or any of the other ingredients of SUSTIVA listed at the end of this leaflet. Contact your doctor or pharmacist for advice.

- if you have severe liver disease.

- if you are currently taking any of the following medicines:
  - astemizole or terfenadine (used to treat allergy symptoms)
  - bepridil (used to treat heart disease)
  - cisapride (used to treat heartburn)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraine and cluster headaches)
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety)

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.

Take special care with 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, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer. 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).

- **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.

  - **changes in body fat.** Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Tell your doctor if you notice changes in your body fat.

  - **bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint...
stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Use in children
SUSTIVA 100 mg hard capsules can be taken by children and adolescents 3 years of age and older and weighing at least 13 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 and cannot tolerate the oral solution (see How to take SUSTIVA).

Taking other medicines
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.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal remedies.

SUSTIVA may interact with other medicines. 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 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
  - a combination medicine containing efavirenz, emtricitabine and tenofovir, which is currently known as ATRIPLA. SUSTIVA should not be taken with ATRIPLA since it contains efavirenz, the active ingredient of SUSTIVA.

- **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 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 need to change your dose of methadone.
- **Sertraline** (a medicine used to treat depression): your doctor may need to change your dose of sertraline.

- **Diltiazem or similar medicines (called calcium channel blockers):** 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 and breast-feeding). 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** (a medicine used to reduce clotting of the blood): your doctor may need to adjust your dose of warfarin.

**Taking SUSTIVA with food and drink**
Taking SUSTIVA on an empty stomach may reduce the undesirable effects.

**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 during pregnancy. If you have taken SUSTIVA 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 may cause dizziness, impaired concentration, and drowsiness. If you are affected, do not drive and do not use any tools or machines.

**Important information about some of the ingredients of SUSTIVA**
This medicinal product contains 342 mg of 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. Individuals with these conditions may take SUSTIVA oral solution, which is free from lactose.
3. **HOW TO TAKE SUSTIVA**

Always take SUSTIVA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- 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.
- 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 Taking other medicines).

Your doctor will give you instructions for proper dosing.

- 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**

- The dose for children weighing 40 kg or more is 600 mg once daily.
- The dose for children weighing less than 40 kg is calculated by body weight and is taken once daily as shown below:

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>SUSTIVA Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to &lt; 15</td>
<td>200</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>250</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>300</td>
</tr>
<tr>
<td>25 to &lt; 32.5</td>
<td>350</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>400</td>
</tr>
</tbody>
</table>

SUSTIVA oral solution is preferred for children who are not able to swallow the capsules. However, if a child does not tolerate the oral solution, the doctor may recommend opening the hard capsule and mixing the contents with a small amount (1-2 teaspoons) of food (e.g., applesauce, grape jelly, yogurt or infant formula). In a taste preference study, efavirenz mixed with grape jelly received the highest rating. The capsules must be opened carefully so that the contents do not spill or escape into the air. Hold the capsule vertically 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 and do not tolerate the oral solution.

**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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, SUSTIVA 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.

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.

The frequency of the side effects listed below is defined using the following conventions:

Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100
Uncommon: affects 1 to 10 users in 1,000
Rare affects 1 to 10 users in 10,000

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

Very common side effects
- skin rash

Common side effects
- abnormal dreams, difficulty concentrating, dizziness, headache, difficulty sleeping, drowsiness, problems with coordination or balance
- stomach pain, diarrhoea, feeling sick (nausea), vomiting
- itching
- tiredness
- feeling worried, feeling depressed

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

**Rare**
- 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.

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

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

**If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

**5. HOW TO STORE SUSTIVA**

Keep out of the reach and sight of children.

Do not use SUSTIVA 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6. FURTHER INFORMATION**

**What 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.
Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

Manufacturer
Bristol-Myers Squibb
Champ "Lachaud", La Goualle
F- 19250 Meymac
France

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

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

Belgique/België/Belgien
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tél/Tel: +32 (0) 800 38693
MSDBelgium_info@merck.com

Luxembourg/Luxemburg
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tél/Tel: +32 (0) 800 38693
MSDBelgium_info@merck.com

България
Мерк Шарп и Доум България ЕООД
Тел.: +359 2 819 3740
info-msdbg@merck.com

Magyarország
MSD Magyarország Kft.
Tel.: +361 888 53 00
hungary MSD@merck.com

Česká republika
Merck Sharp & Dohme IDEA, Inc., org. sl.
Tel.: +420 233 010 111
msd_cr@merck.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: +357 22866700
malta_info@merck.com

Danmark
Merck Sharp & Dohme
Tlf: +45 43 28 77 66
dkmail@merck.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800-9999000
medicalinfo.nl@merck.com

Deutschland
Bristol-Myers Squibb GmbH & Co. KGaA
Tel: +49 89 121 42-0

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
msdnorge@msd.no
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.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What SUSTIVA is and what it is used for
2. Before you take SUSTIVA
3. How to take SUSTIVA
4. Possible side effects
5. How to store SUSTIVA
6. Further information

1. WHAT SUSTIVA IS AND WHAT IT IS USED FOR

SUSTIVA 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) infection by reducing the amount of the virus in blood.

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.

2. BEFORE YOU TAKE SUSTIVA

Do not take SUSTIVA
- if you are allergic (hypersensitive) to efavirenz or any of the other ingredients of SUSTIVA listed at the end of this leaflet. Contact your doctor or pharmacist for advice.
- if you have severe liver disease.
- if you are currently taking any of the following medicines:
  - astemizole or terfenadine (used to treat allergy symptoms)
  - bepridil (used to treat heart disease)
  - cisapride (used to treat heartburn)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraine and cluster headaches)
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety)

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.

Take special care with 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, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer. 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).

- **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.
  - **changes in body fat.** Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Tell your doctor if you notice changes in your body fat.
  - **bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint
stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Use in children
SUSTIVA 200 mg hard capsules can be taken by children and adolescents 3 years of age and older and weighing at least 13 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 and cannot tolerate the oral solution (see How to take SUSTIVA).

Taking other medicines
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.

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SUSTIVA may interact with other medicines. 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 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
  - a combination medicine containing efavirenz, emtricitabine and tenofovir, which is currently known as ATRIPLA. SUSTIVA should not be taken with ATRIPLA since it contains efavirenz, the active ingredient of SUSTIVA.

- **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 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 need to change your dose of methadone.
- **Sertraline** (a medicine used to treat depression): your doctor may need to change your dose of sertraline.

- **Diltiazem or similar medicines (called calcium channel blockers):** when you start taking SUSTIVA, your doctor may need to adjust your dose of the calcium channel blocker.

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- **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 and breast-feeding). 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** (a medicine used to reduce clotting of the blood): your doctor may need to adjust your dose of warfarin.

**Taking SUSTIVA with food and drink**
Taking SUSTIVA on an empty stomach may reduce the undesirable effects.

**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 during pregnancy. If you have taken SUSTIVA 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 may cause dizziness, impaired concentration, and drowsiness. If you are affected, do not drive and do not use any tools or machines.

**Important information about some of the ingredients of SUSTIVA**
This medicinal product contains 342 mg of 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. Individuals with these conditions may take SUSTIVA oral solution, which is free from lactose.
3. **HOW TO TAKE SUSTIVA**

Always take SUSTIVA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- 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.
- 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 Taking other medicines).

Your doctor will give you instructions for proper dosing.

- 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**

- The dose for children weighing 40 kg or more is 600 mg once daily.
- The dose for children weighing less than 40 kg is calculated by body weight and is taken once daily as shown below:

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to &lt; 15</td>
<td>200</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>250</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>300</td>
</tr>
<tr>
<td>25 to &lt; 32.5</td>
<td>350</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>400</td>
</tr>
</tbody>
</table>

SUSTIVA oral solution is preferred for children who are not able to swallow the capsules. However, if a child does not tolerate the oral solution, the doctor may recommend opening the hard capsule and mixing the contents with a small amount (1-2 teaspoons) of food (e.g., applesauce, grape jelly, yogurt or infant formula). In a taste preference study, efavirenz mixed with grape jelly received the highest rating. The capsules must be opened carefully so that the contents do not spill or escape into the air. Hold the capsule vertically 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 and do not tolerate the oral solution.

**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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, SUSTIVA 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.

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.

The frequency of the side effects listed below is defined using the following conventions:

- **Very common:** affects more than 1 user in 10
- **Common:** affects 1 to 10 users in 100
- **Uncommon:** affects 1 to 10 users in 1,000
- **Rare:** affects 1 to 10 users in 10,000

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

**Very common side effects**
- skin rash

**Common side effects**
- abnormal dreams, difficulty concentrating, dizziness, headache, difficulty sleeping, drowsiness, problems with coordination or balance
- stomach pain, diarrhoea, feeling sick (nausea), vomiting
- itching
- tiredness
- feeling worried, feeling depressed

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

**Rare**
- 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.

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

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

**If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

5. **HOW TO STORE SUSTIVA**

Keep out of the reach and sight of children.

Do not use SUSTIVA 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What 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.
Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

Manufacturer
Bristol-Myers Squibb
Champ "Lachaud", La Goualle
F- 19250 Meymac
France

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

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

Belgique/België/Belgien
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tél/Tel: +32 (0) 800 38693
MSDBelgium_info@merck.com

Magyarország
MSD Magyarország Kft.
Tel.: +361 888 53 00
hungary_msd@merck.com

Danmark
Merck Sharp & Dohme
Tlf: +45 43 28 77 66
dkmail@merck.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800-9999000
medicalinfo.nl@merck.com

Deutschland
Bristol-Myers Squibb GmbH & Co. KGaA
Tel: +49 89 121 42-0

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
msdnorge@msd.no
This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.
SUSTIVA 30 mg/ml oral solution

efavirenz

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What SUSTIVA is and what it is used for
2. Before you take SUSTIVA
3. How to take SUSTIVA
4. Possible side effects
5. How to store SUSTIVA
6. Further information

1. WHAT SUSTIVA IS AND WHAT IT IS USED FOR

SUSTIVA 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) infection by reducing the amount of the virus in blood.

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.

2. BEFORE YOU TAKE SUSTIVA

Do not take SUSTIVA
- if you are allergic (hypersensitive) to efavirenz or any of the other ingredients of SUSTIVA listed at the end of this leaflet. Contact your doctor or pharmacist for advice.

- if you have severe liver disease.

- if you are currently taking any of the following medicines:
  - astemizole or terfenadine (used to treat allergy symptoms)
  - bepridil (used to treat heart disease)
  - cisapride (used to treat heartburn)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraine and cluster headaches)
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety)

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.

Take special care with 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, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer. 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).

• **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.
  - changes in body fat. Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Tell your doctor if you notice changes in your body fat.
  - bone problems. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint
stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Use in children
SUSTIVA oral solution can be taken by children 3 years of age and older (see How to take SUSTIVA).

Taking other medicines
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.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal remedies.

SUSTIVA may interact with other medicines. 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 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
  - a combination medicine containing efavirenz, emtricitabine and tenofovir, which is currently known as ATRIPLA. SUSTIVA should not be taken with ATRIPLA since it contains efavirenz, the active ingredient of SUSTIVA.

- **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 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 need to change your dose of methadone.

- **Sertraline** (a medicine used to treat depression): your doctor may need to change your dose of sertraline.
- **Diltiazem or similar medicines (called calcium channel blockers)**: 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 and breast-feeding). 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** (a medicine used to reduce clotting of the blood): your doctor may need to adjust your dose of warfarin.

**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 during pregnancy. If you have taken SUSTIVA 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 may cause dizziness, impaired concentration, and drowsiness. If you are affected, do not drive and do not use any tools or machines.

3. **HOW TO TAKE SUSTIVA**

Always take SUSTIVA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- SUSTIVA oral solution may be taken with or without food.
- The dose for adults is 24 ml once daily.

- The dose for SUSTIVA may need to be increased or decreased if you are also taking certain medicines (see Taking other medicines).

The dose of SUSTIVA oral solution in mg is not the same as for SUSTIVA hard capsules or film-coated tablets. Your doctor will give you instructions for proper dosing.
- 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
- The dose for children weighing 40 kg or more is 24 ml once daily.
- The dose for children weighing less than 40 kg is calculated by body weight and is taken once daily as shown below:

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>SUSTIVA oral solution (30 mg/ml) Dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children 3 - &lt; 5 years</td>
</tr>
<tr>
<td>13 to &lt; 15</td>
<td>12</td>
</tr>
<tr>
<td>15 to &lt; 20</td>
<td>13</td>
</tr>
<tr>
<td>20 to &lt; 25</td>
<td>15</td>
</tr>
<tr>
<td>25 to &lt; 32.5</td>
<td>17</td>
</tr>
<tr>
<td>32.5 to &lt; 40</td>
<td>-</td>
</tr>
<tr>
<td>≥ 40</td>
<td>-</td>
</tr>
</tbody>
</table>

The dose of SUSTIVA oral solution must be measured using the oral syringe supplied in the carton.

- On first use, the bottle adapter must be fitted into the neck of the bottle. To do this, remove the child-resistant cap and the foil seal. The bottle adapter, which is already fixed to the nozzle of the syringe, can then be fitted into the neck of the bottle and pressed firmly down.

- Separate the syringe from the adapter. The adapter should now fit closely to the neck so that the cap can be replaced without removing it.

- With the bottle upright, fit the tip of the syringe into the bottle adapter.
- Turn the bottle upside down with the syringe still in place. Hold the bottle and the syringe firmly in one hand and with the other hand pull back the plunger slightly beyond the mark for the dose required. If air bubbles appear in the syringe, keep the bottle upside down and slowly push in the plunger and pull it back again. Repeat until there are no bubbles in the syringe.

- To measure the dose accurately, keep the bottle upside down and push the plunger in slowly until the top of the black ring (the edge nearest the syringe tip) lines up with the dose. Turn the bottle the right way up and remove the syringe. Wipe the adapter and replace the cap tightly over it.

- Before giving the dose of the oral solution make sure that the patient is sitting or standing upright. Put the tip of the syringe just inside the mouth, pointing it towards the cheek. Press the plunger slowly to allow time for the medicine to be swallowed. Rapid squirting into the mouth may cause choking.

After use, soak the syringe in warm soapy water for at least a minute. Draw the warm soapy water into the syringe until full and then empty completely. Repeat at least three times. Remove the plunger rod from the barrel and thoroughly rinse both parts with warm running water. If parts of the syringe are not clean, repeat the cleaning instructions. Allow the parts to dry completely prior to reassembly. Do not put the syringe in a dishwasher.

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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, SUSTIVA 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.
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. 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.

Diarrhoea occurred in children who took SUSTIVA oral solution and nelfinavir in combination with other antiretroviral medicines.

The frequency of the side effects listed below is defined using the following conventions:

- **Very common**: affects more than 1 user in 10
- **Common**: affects 1 to 10 users in 100
- **Uncommon**: affects 1 to 10 users in 1,000
- **Rare**: affects 1 to 10 users in 10,000

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

**Very common side effects**
- skin rash

**Common side effects**
- abnormal dreams, difficulty concentrating, dizziness, headache, difficulty sleeping, drowsiness, problems with coordination or balance
- stomach pain, diarrhoea, feeling sick (nausea), vomiting
- itching
- tiredness
- feeling worried, feeling depressed

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

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

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

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SUSTIVA

Keep out of the reach and sight of children.

Do not use SUSTIVA 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. The bottle of SUSTIVA oral solution should be used within one month after first opening.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What SUSTIVA contains
- Each ml of SUSTIVA oral solution contains 30 mg of the active substance efavirenz.
- The other ingredients are: medium chain triglycerides, benzoic acid (E210) and strawberry/mint flavour.

What SUSTIVA looks like and contents of the pack
SUSTIVA 30 mg/ml oral solution is supplied in bottles of 180 ml.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

Manufacturer
Bristol-Myers Squibb
Champ "Lachaud", La Goualle
F- 19250 Meymac
France

Lawrence Laboratories
Unit 12 Distribution Centre, Shannon Free Zone, Shannon Industrial Estate, Co. Clare
Ireland
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

Belgique/België/Belgien
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tel./Tel: +32 (0) 800 38693
MSDBelgium_info@merck.com

Luxembourg/Luxemburg
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tel./Tel: +32 (0) 800 38693
MSDBelgium_info@merck.com

Magyarország
MSD Magyarország Kft.
Tel.: +361 888 53 00
hungary_msd@merck.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: +357 22866700
malta_info@merck.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800-9999000
medicalinfo.nl@merck.com

Österreich
Merck Sharp & Dohme Ges.m.b.H
Tel: +43 (0) 1 26 044
msd-medizin@merck.com

Polska
MSD Polska Sp.z o.o.
Tel.: +48 22 549 51 00
msdpolska@merck.com

Portugal
Merck Sharp & Dohme, Lda
Tel: +351 21 446 57 00
informacao_doente@merck.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel: + 4021 529 29 00
msdromania@merck.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: + 386 1 5204201
msd_slovenia@merck.com
Ísland
Icepharma hf.
Simi: +354 540 8000
ISmail@merck.com

Italia
Bristol-Myers Squibb S.r.l.
Tel: +39 06 50 39 61

Kύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ.: +357 22866700
cyprus_info@merck.com

Latvija
SIA “Merck Sharp & Dohme Latvija”.
Tel: +371 67364 224
msd_lv@merck.com

Lietuva
UAB “Merck Sharp & Dohme”
Tel.: +370 5 278 02 47
msd_lietuva@merck.com

Slovenská republika
Merck Sharp & Dohme IDEA, Inc.
Tel.: +421 2 58282010
msd_sk@merck.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0) 9 804650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: +46 (0) 8 626 1400
medicinskinfo@merck.com

United Kingdom
Bristol-Myers Squibb Pharmaceuticals Ltd.
Tel: +44 (0800) 731 1736

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
SUSTIVA 600 mg film-coated tablets
efavirenz

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What SUSTIVA is and what it is used for
2. Before you take SUSTIVA
3. How to take SUSTIVA
4. Possible side effects
5. How to store SUSTIVA
6. Further information

1. WHAT SUSTIVA IS AND WHAT IT IS USED FOR

SUSTIVA 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) infection by reducing the amount of the virus in blood.

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.

2. BEFORE YOU TAKE SUSTIVA

Do not take SUSTIVA

- if you are allergic (hypersensitive) to efavirenz or any of the other ingredients of SUSTIVA listed at the end of this leaflet. Contact your doctor or pharmacist for advice.

- if you have severe liver disease.

- if you are currently taking any of the following medicines:
  - astemizole or terfenadine (used to treat allergy symptoms)
  - bepridil (used to treat heart disease)
  - cisapride (used to treat heartburn)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraine and cluster headaches)
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety)

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.

Take special care with 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, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer. 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).

- **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.

  - **changes in body fat.** Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Tell your doctor if you notice changes in your body fat.

  - **bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint
stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Use in children
SUSTIVA film-coated tablets are not suitable for children weighing less than 40 kg.

Taking other medicines
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.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal remedies.

SUSTIVA may interact with other medicines. 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 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
  - a combination medicine containing efavirenz, emtricitabine and tenofovir, which is currently known as ATRIPLA. SUSTIVA should not be taken with ATRIPLA since it contains efavirenz, the active ingredient of SUSTIVA.

- **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 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 need to change your dose of methadone.

- **Sertraline** (a medicine used to treat depression): your doctor may need to change your dose of sertraline.
Diltiazem or similar medicines (called calcium channel blockers): 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 and breast-feeding). 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 (a medicine used to reduce clotting of the blood): your doctor may need to adjust your dose of warfarin.

Taking SUSTIVA with food and drink
Taking SUSTIVA on an empty stomach, may reduce the undesirable effects.

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 during pregnancy. If you have taken SUSTIVA 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 may cause dizziness, impaired concentration, and drowsiness. If you are affected, do not drive and do not use any tools or machines.

Important information about some of the ingredients of SUSTIVA
This medicinal product contains 250 mg of 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. Individuals with these conditions may take SUSTIVA oral solution, which is free from lactose.
3. **HOW TO TAKE SUSTIVA**

Always take SUSTIVA exactly as your doctor has told you. It is recommended that the tablet be swallowed whole with water. You should check with your doctor or pharmacist if you are not sure. Your doctor will give you instructions for proper dosing.

- 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.
- 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 Taking other medicines).
- 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**

- 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 product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, SUSTIVA 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.

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.

The frequency of the side effects listed below is defined using the following conventions:

- **Very common**: affects more than 1 user in 10
- **Common**: affects 1 to 10 users in 100
- **Uncommon**: affects 1 to 10 users in 1,000
- **Rare**: affects 1 to 10 users in 10,000

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

**Very common side effects**
- skin rash

**Common side effects**
- abnormal dreams, difficulty concentrating, dizziness, headache, difficulty sleeping, drowsiness, problems with coordination or balance
- stomach pain, diarrhoea, feeling sick (nausea), vomiting
- itching
- tiredness
- feeling worried, feeling depressed

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

**Rare**
- 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.

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

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, increased fat levels in the blood (hyperlipaemia) and resistance to insulin. Your doctor will test for these changes.
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5.  HOW TO STORE SUSTIVA

Keep out of the reach and sight of children.

Do not use SUSTIVA 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.  FURTHER INFORMATION

What 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 90 (3 x 30 x 1) tablets in aluminium/PVC perforated unit dose blisters. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park, Sanderson Road
Uxbridge UB8 1DH
United Kingdom

Manufacturer
Bristol-Myers Squibb
Champ "Lachaud", La Goualle
F- 19250 Meymac
France

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

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

Belgique/België/Belgien
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tél/Tel: +32 (0) 800 38693

Luxembourg/Luxemburg
Merck Sharp & Dohme B.V.
Succursale belge/Belgisch bijhuis
Tél/Tel: +32 (0) 800 38693
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