ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. THE MEDICINAL PRODUCT

SUSTIVA 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg efavirenz

For excipients see 6.1 List of excipients

3. PHARMACEUTICAL FORM

Hard capsule

SUSTIVA 50 mg hard capsules are dark yellow and white, printed with “SUSTIVA” on the dark yellow cap and with “50 mg” on the white body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUSTIVA is indicated in antiviral combination treatment of 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 protease inhibitors has not been documented, there are at present insufficient data on the efficacy of subsequent use of protease inhibitor based combination therapy after failure of regimens containing SUSTIVA.

See 5.1 Pharmacodynamic properties: Pharmacodynamic effects for a summary of clinical and pharmacodynamic information.

4.2 Posology and method of administration

Concomitant antiretroviral therapy: SUSTIVA must be given in combination with other antiretroviral medications (see 4.5 Interactions with other medicinal products).

SUSTIVA may be taken with or without food (see 5.2 Pharmacokinetic properties: The effect of food).
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 4.8 Undesirable effects).

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

**Adults:** The recommended dosage of SUSTIVA in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily.

**Adolescents and children (3 to 17 years):** The recommended dose of SUSTIVA in combination with a protease inhibitor 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. SUSTIVA has not been studied in children under the age of 3 years or children weighing less than 13 kg.

### 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>
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<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>
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</table>

**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 4.4 Special warnings and special precautions for use: Special populations).

**Liver disease:** Patients with mild to moderate liver disease may be treated cautiously with efavirenz, 600 mg once daily. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms (see 4.3 Contra-indications and 4.4 Special warnings and special precautions for use: Special populations).

### 4.3 Contraindications

SUSTIVA is contraindicated in patients with clinically significant hypersensitivity to the active substance or to any of the excipients.

Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Grade C) (see 5.2 Pharmacokinetic properties).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, or triazolam because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening
undesirable effects [e.g., cardiac arrhythmias, prolonged sedation or respiratory depression] (see 4.5 Interactions with other medicinal products).

4.4 Special warnings and special 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. Therapy with efavirenz must always be initiated in combination with one or more new antiretroviral agent(s) to which the patient has not been previously exposed. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance. Resistant virus emerges rapidly when efavirenz is administered as monotherapy.

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 medication in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medications. The antiretroviral medications 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.

Skin 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 0.14%. 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 anti-retroviral agents to avoid development of resistant virus (see 4.8 Undesirable effects).

Rash was reported in 23 of 57 children (40%) treated with SUSTIVA and was severe in four patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Patients who discontinued treatment with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) due to rash may be at higher risk of developing rash during treatment with efavirenz.

Nervous system symptoms: Nervous system symptoms have been reported in clinical studies with efavirenz (see 4.8 Undesirable effects). In addition, there have been reports (approximately 1-2 per thousand patients treated with efavirenz) of psychosis-like reactions, such as delusions and inappropriate behaviour, predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempt) has also been infrequently reported in both efavirenz-treated and control-treated patients, particularly in patients with a previous history of depression. Patients
should be advised that if they experience these symptoms they should contact their doctor immediately because discontinuation of efavirenz may be required.

**Special populations:** Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild-to-moderate liver disease. A 600 mg dose once daily is recommended. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see 4.2 Posology and method of administration).

In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with 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 unknown risks of significant liver toxicity (see 4.8 Undesirable effects).

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 4.2 Posology and method of administration). There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

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

Efavirenz has not been evaluated in children below 3 years of age or who weigh less than 13 kg.

**Cholesterol:** Monitoring of cholesterol should be considered in patients treated with efavirenz (see 4.8 Undesirable effects).

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

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

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, or triazolam (see 4.3 Contraindications).

**Concomitant antiretroviral agents**

*Nelfinavir:* The AUC and \( C_{\text{max}} \) of nelfinavir are increased by 20% and 21%, respectively, when given with efavirenz. The combination was generally well tolerated and no dose adjustment is necessary when nelfinavir is administered in combination with efavirenz.
**Indinavir:** When indinavir (800 mg every 8 hours) was given with efavirenz (200 mg every 24 hours), the indinavir AUC and C_{max} were decreased by approximately 31% and 16%, respectively, as a result of enzyme induction. The degree of reduction in indinavir levels may be greater when efavirenz 600 mg every 24 hours is given. Higher doses of indinavir offset the metabolic induction by efavirenz. At present the recommendation is to increase the dose of indinavir from 800 mg every 8 hours to 1,000 mg every 8 hours when efavirenz and indinavir are co-administered. No adjustment of the dose of efavirenz is necessary when given with indinavir.

**Ritonavir:** When efavirenz 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) were studied in uninfected volunteers the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.

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

**Saquinavir/ritonavir:** No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir.

**Nucleoside analogue reverse transcriptase inhibitors (NRTIs):** Studies of the interaction between efavirenz and the combination of zidovudine and lamivudine were performed in HIV infected patients. No clinically significant pharmacokinetic interactions were observed. Specific interaction studies have not been performed with efavirenz and other NRTIs. Clinically significant interactions would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

**Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** No studies have been performed with efavirenz in combination with other non-nucleoside reverse transcriptase inhibitors and the potential for pharmacokinetic or pharmacodynamic interactions is unknown.
**Antimicrobial agents:**

**Rifamycins:** Rifampicin reduced efavirenz AUC by 26% and C_max by 20% in uninfected volunteers. The dose of efavirenz must be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with efavirenz. Rifabutin has not been studied in combination with efavirenz.

**Macrolide antibiotics:**

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

**Clarithromycin:** Co-administration of 400 mg of efavirenz once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C_max of clarithromycin decreased 39% and 26%, respectively, while the AUC and C_max of the active clarithromycin hydroxymetabolite were increased 34% and 49%, respectively, when used in combination with efavirenz. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin should be considered.

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

**Antifungal agents:**

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

**Other interactions**

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

**Oral contraceptives:** Only the ethinyloestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinyloestradiol was increased (37%) by efavirenz. No significant changes were observed in C_max of ethinyloestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyloestradiol on efavirenz C_max or AUC was observed. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

**Phenytoin and phenobarbital:** No data are available on the potential interactions of efavirenz with phenytoin or phenobarbital. When efavirenz is administered concomitantly with phenytoin or phenobarbital there is the potential for reduction in the plasma concentrations of each agent.
4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available for efavirenz. Studies in animals have shown reproductive toxicity including marked teratogenic effects (see 5.3 Preclinical safety data). Therefore, efavirenz should not be used during pregnancy unless clearly necessary (the potential benefit to the mother outweighs the potential risk to the foetus and there are no other appropriate treatment options). Pregnancy should be avoided in women receiving efavirenz. Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives).

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. Some health experts recommend that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

Efavirenz has not been specifically evaluated for possible effects on the ability to drive a car or operate machinery. 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

Efavirenz has been studied in over 2,000 patients. In a subset of 413 patients who received 600 mg efavirenz daily in combination with protease inhibitors and/or NRTIs in controlled clinical studies, the most frequently reported treatment related undesirable effects of at least moderate severity were rash (13.1%), nausea (10.4%), dizziness (9.2%), diarrhoea (6.8%), headache (6.3%), insomnia (6.1%), fatigue (5.6%) and impaired concentration (5.3%). Nausea was reported at higher frequency and diarrhoea was reported with about equal frequency in the control groups. The most notable undesirable effects associated with efavirenz are rash and nervous system symptoms (see 4.4 Special warnings and special precautions for use).

A few cases of pancreatitis have been described although causal relationship with efavirenz has not been established.

The type and frequency of undesirable effects in children was generally similar to that of adult patients with the exception that rash was reported more frequently in children and was more often of higher grade than in adults.

Rash: In clinical studies, 28% of patients treated with 600 mg of efavirenz experienced skin rash compared with 18% of patients treated in control groups. Skin rash was considered treatment related in 18% of patients treated with efavirenz. Severe rash occurred in 0.7% of patients treated with efavirenz and 1.7% discontinued therapy because of rash. In over 2,000 patients treated with efavirenz, the incidence of erythema multiforme or Stevens-Johnson Syndrome was 0.14%.
Rash was reported in 23 of 57 children (40%) treated with efavirenz and was severe in 4 patients (7%). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

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

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

**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. In controlled clinical studies where 600 mg efavirenz was administered with other antiretroviral agents, 22.8% of patients experienced nervous system symptoms of moderate-to-severe intensity compared to 10.1% of patients receiving control regimens. These symptoms were severe in 2.9% of patients receiving efavirenz 600 mg daily and in 1.3% of patients receiving control regimens. Additionally psychosis-like reactions have been observed in approximately 1 – 2 per 1,000 patients treated with efavirenz. In clinical studies 2.7% of patients treated with 600 mg of efavirenz discontinued therapy because of nervous system symptoms. Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2-4 weeks. In 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. 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 4.2 Posology and method of administration). Dose reduction or splitting the daily dose has not been shown to provide benefit.

**Laboratory test abnormalities:**

**Liver enzymes:** Elevations of AST to greater than five times the upper limit of the normal range were seen in 2% of 391 patients treated with 600 mg of efavirenz and 3% of 283 patients treated with control regimens. Elevations of ALT to greater than five times the upper limit of normal were seen in 3% and 2% of patients treated with 600 mg of efavirenz and control regimens, respectively. In 53 patients treated with 600 mg of efavirenz who were seropositive for Hepatitis B and/or C, 6% developed AST levels and 13% developed ALT levels of this magnitude. In 41 patients seropositive for Hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 2% developed ALT elevations to these levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4% of all patients treated with 600 mg of efavirenz and in 11% of patients seropositive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 2%, irrespective of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity (see 4.4 Special warnings and special precautions for use).

**Lipids:** Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving efavirenz. Modest elevations of serum triglycerides and cholesterol have also been observed in patients receiving efavirenz; however the significance of these findings
is unknown, in part because samples were obtained from non-fasting patients. The effect of efavirenz on total, LDL, and HDL cholesterol in patients receiving long term therapy with efavirenz has not been evaluated (see 4.4 Special warnings and special precautions for use).

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.

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.
PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HIV-1 specific non-nucleoside reverse-transcriptase inhibitor (NNRTI).
ATC code: J05A G 03

Mechanism of action: Efavirenz is a non-nucleoside reverse transcriptase inhibitor (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. Substitutions at RT positions 100, 101, 108, 138, 188 or 190 were also observed, but at lower frequencies, and often only in combination with K103N. The K103N substitution was not observed in patient samples obtained prior to treatment with efavirenz. 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 protease inhibitors 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.

**Pharmacodynamic effects**

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts <50 cells/mm³, or in protease inhibitor or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited. Long term efficacy and safety studies are ongoing.

Controlled clinical studies of up to 24 weeks duration with efavirenz in combination with NRTIs and/or protease inhibitors 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. In Studies 006, 020 and ACTG 364 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.

Efficacy results 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 studies 006, 020 and ACTG 364**

| Study Number/Treatment Regimens ** |  |  |  |  |  |  |
|----------------------------------|---|---|---|---|---|
| Study Number/Treatment Regimens ** | n | % | (95% C.I.**) | % | (95% C.I.) | Mean change from baseline-CD4 cell counts (S.E.M.**) |
| Study 006 24 weeks |  |  |  |  |  |  |
| EFV+ZDV+3TC | 15 | 75 | (68, 82) | 58 | (50, 66) | 128 (9.1) |
| EFV+IDV | 14 | 66 | (58, 73) | 46 | (38, 54) | 134 (11.9) |
| IDV+ZDV+3TC | 14 | 56 | (48, 64) | 43 | (35, 52) | 116 (10.6) |
| Study 020 24 weeks |  |  |  |  |  |  |
| EFV+IDV+NRTIs | 92 | 64 | (53, 74) | 54 | (44, 65) | 115 (11.7) |
| IDV+NRTIs | 92 | 52 | (41, 63) | 36 | (25, 46) | 85 (14.4) |
| Study ACTG 364 24 weeks |  |  |  |  |  |  |
EFV+NFV+NRTIs 64 78 (67, 89) --- --- 46 (26.1)
EFV+NRTIs 65 60 (48, 72) --- --- 81 (15.3)
NFV+NRTIs 66 45 (33, 58) --- --- 70 (13.8)

* < 500 copies/ml for ACTG 364
** EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir; ---, not performed; S.E.M., standard error of the mean; NC=F, noncompleter=failure; C.I., confidence interval

Study 006 evaluated 450 patients not previously treated with protease inhibitors, NNRTIs, or lamivudine. This study was designed to test the equivalence of the regimens. The higher rate of premature discontinuations as a result of adverse experiences in the control group of this open-label study contributed to the differences in the responder rates.

Study 020 evaluated 184 patients who had been treated with NRTIs but not with protease inhibitors 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.

Study ACTG 364 evaluated 195 patients who had been treated with NRTIs but not with protease inhibitors or NNRTIs.

**Paediatric trial:** ACTG 382 is an ongoing 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 20 weeks was 61% (95%, C.I. 48, 74), and the mean CD4 cell counts were increased by 100 ± 37.5 cells/mm³ from baseline.

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 patients receiving efavirenz 600 mg once daily, mean steady state C<sub>max</sub> was 12.9 μM, steady state C<sub>min</sub> was 5.6 μM, and AUC was 184 μM·h.

**The effect of food:** In uninfected volunteers, meals of normal composition had no appreciable effect on bioavailability of 100 mg of efavirenz administered twice a day for 10 days with meals. The relative bioavailability of a single 1,200 mg dose of efavirenz in uninfected volunteers was increased 50% following a high fat meal.
**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 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 of 40-55 hours (single dose half-life 52-76 hours).

**Elimination:** Efavirenz has a relatively long terminal half-life of 52 to 76 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.

In the single patient studied with severe hepatic impairment (Child Pugh Grade C), half life was doubled indicating a potential for a much greater degree of accumulation.

**Paediatric pharmacokinetics:** In 48 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 14.2 $\mu$M, steady state $C_{\text{min}}$ was 5.6 $\mu$M, and AUC was 218 $\mu$M·h. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

**Gender, race, elderly:** Pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied. Although limited data suggest that 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.

**5.3 Preclinical safety data**

Long-term carcinogenicity studies of efavirenz in rats and mice are in progress.

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 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.

Increases in ALT activity were observed in cynomolgus monkeys given efavirenz at doses corresponding to the exposure levels seen in humans. Minimal biliary hyperplasia was observed in four of eight cynomolgus monkeys given efavirenz for 1 year at a dose resulting in mean AUC values approximately 5 fold greater than those in humans given the recommended dose. Biliary fibrosis has been observed in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium lauryl sulphate, lactose monohydrate, magnesium stearate and sodium starch glycolate.

The capsule shell: gelatine, sodium lauryl sulphate, yellow iron oxide (E172), titanium dioxide (E171) and silicon dioxide.

Printing ink: cochineal carminic acid (E120), indigo carmine (E132), and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

18 months.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and content of container

HDPE bottles with a child-resistant polypropylene closure. Bottles of 30 hard capsules.

6.6 Instructions for use and handling
No special requirements.

7. AUTHORISATION HOLDER

DuPont Pharmaceuticals Limited
Wedgwood Way
Stevenage
Hertfordshire, SG1 4QN
United Kingdom

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

SUSTIVA 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg efavirenz

For excipients see 6.1 List of excipients

3. PHARMACEUTICAL FORM

Hard capsule

SUSTIVA 100 mg hard capsules are 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 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 protease inhibitors has not been documented, there are at present insufficient data on the efficacy of subsequent use of protease inhibitor based combination therapy after failure of regimens containing SUSTIVA.

See 5.1 Pharmacodynamic properties: Pharmacodynamic effects for a summary of clinical and pharmacodynamic information.

4.2 Posology and method of administration

Concomitant antiretroviral therapy: SUSTIVA must be given in combination with other antiretroviral medications (see 4.5 Interactions with other medicinal products).

SUSTIVA may be taken with or without food (see 5.2 Pharmacokinetic properties: The effect of food).
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 4.8 Undesirable effects).

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

**Adults:** The recommended dosage of SUSTIVA in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily.

**Adolescents and children (3 to 17 years):** The recommended dose of SUSTIVA in combination with a protease inhibitor 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. SUSTIVA has not been studied in children under the age of 3 years or children weighing less than 13 kg.

**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>

**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 4.4 Special warnings and special precautions for use: Special populations).

**Liver disease:** Patients with mild to moderate liver disease may be treated cautiously with efavirenz, 600 mg once daily. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms (see 4.3 Contra-indications and 4.4 Special warnings and special precautions for use: Special populations).

### 4.3 Contra-indications

SUSTIVA is contraindicated in patients with clinically significant hypersensitivity to the active substance or to any of the excipients.

Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Grade C) (see 5.2 Pharmacokinetic properties).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, or triazolam because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening
undesirable effects [e.g., cardiac arrhythmias, prolonged sedation or respiratory depression] (see 4.5 Interactions with other medicinal products).

4.4 Special warnings and special 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. Therapy with efavirenz must always be initiated in combination with one or more new antiretroviral agent(s) to which the patient has not been previously exposed. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance. Resistant virus emerges rapidly when efavirenz is administered as monotherapy.

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 medication in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medications. The antiretroviral medications 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.

Skin 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 0.14%. 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 anti-retroviral agents to avoid development of resistant virus (see 4.8 Undesirable effects).

Rash was reported in 23 of 57 children (40%) treated with SUSTIVA and was severe in four patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Patients who discontinued treatment with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) due to rash may be at higher risk of developing rash during treatment with efavirenz.

Nervous system symptoms: Nervous system symptoms have been reported in clinical studies with efavirenz (see 4.8 Undesirable effects). In addition, there have been reports (approximately 1-2 per thousand patients treated with efavirenz) of psychosis-like reactions, such as delusions and inappropriate behaviour, predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both efavirenz-treated and control-treated patients, particularly in patients with a previous history of depression. Patients
should be advised that if they experience these symptoms they should contact their doctor immediately because discontinuation of efavirenz may be required.

**Special populations:** Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild-to-moderate liver disease. A 600 mg dose once daily is recommended. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see 4.2 Posology and method of administration).

In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with 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 unknown risks of significant liver toxicity (see 4.8 Undesirable effects).

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 4.2 Posology and method of administration). There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

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

Efavirenz has not been evaluated in children below 3 years of age or who weigh less than 13 kg.

**Cholesterol:** Monitoring of cholesterol should be considered in patients treated with efavirenz (see 4.8 Undesirable effects).

4.5 Interaction with other medicinal products and other forms of interaction

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

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, or triazolam (see 4.3 Contraindications).

**Concomitant antiretroviral agents**

**Nelfinavir:** The AUC and C_max of nelfinavir are increased by 20% and 21%, respectively when given with efavirenz. The combination was generally well tolerated and no dose adjustment is necessary when nelfinavir is administered in combination with efavirenz.
**Indinavir:** When indinavir (800 mg every 8 hours) was given with efavirenz (200 mg every 24 hours), the indinavir AUC and C$_{\text{max}}$ were decreased by approximately 31% and 16%, respectively, as a result of enzyme induction. The degree of reduction in indinavir levels may be greater when efavirenz 600 mg every 24 hours is given. Higher doses of indinavir offset the metabolic induction by efavirenz. At present the recommendation is to increase the dose of indinavir from 800 mg every 8 hours to 1,000 mg every 8 hours when efavirenz and indinavir are co-administered. No adjustment of the dose of efavirenz is necessary when given with indinavir.

**Ritonavir:** When efavirenz 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) were studied in uninfected volunteers the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.

**Saquinavir:** When saquinavir (1,200 mg given 3 times a day, soft capsule formulation) was given with efavirenz, the saquinavir AUC and C$_{\text{max}}$ were decreased by 62% and 50% respectively. Use of efavirenz in combination with saquinavir as the sole protease inhibitor is not recommended.

**Saquinavir/ritonavir:** No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir.

**Nucleoside analogue reverse transcriptase inhibitors (NRTIs):** Studies of the interaction between efavirenz and the combination of zidovudine and lamivudine were performed in HIV infected patients. No clinically significant pharmacokinetic interactions were observed. Specific interaction studies have not been performed with efavirenz and other NRTIs. Clinically significant interactions would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

**Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** No studies have been performed with efavirenz in combination with other non-nucleoside reverse transcriptase inhibitors and the potential for pharmacokinetic or pharmacodynamic interactions is unknown.

**Antimicrobial agents:**

**Rifamycins:** Rifampicin reduced efavirenz AUC by 26% and C$_{\text{max}}$ by 20% in uninfected volunteers. The dose of efavirenz must be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with efavirenz. Rifabutin has not been studied in combination with efavirenz.

**Macrolide antibiotics:**

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

**Clarithromycin:** Co-administration of 400 mg of efavirenz once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C$_{\text{max}}$ of clarithromycin decreased 39% and 26%, respectively, while the AUC and C$_{\text{max}}$ of the active clarithromycin
hydroxymetabolite were increased 34% and 49%, respectively, when used in combination with efavirenz. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin should be considered.

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

**Antifungal agents:**

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

**Other interactions**

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

**Oral contraceptives:** Only the ethinyloestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinyloestradiol was increased (37%) by efavirenz. No significant changes were observed in C\text{max} of ethinyloestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyloestradiol on efavirenz C\text{max} or AUC was observed. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

**Phenytoin and phenobarbital:** No data are available on the potential interactions of efavirenz with phenytoin or phenobarbital. When efavirenz is administered concomitantly with phenytoin or phenobarbital there is the potential for reduction in the plasma concentrations of each agent.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available for efavirenz. Studies in animals have shown reproductive toxicity including marked teratogenic effects (see 5.3 Preclinical safety data). Therefore, efavirenz should not be used during pregnancy unless clearly necessary (the potential benefit to the mother outweighs the potential risk to the foetus and there are no other appropriate treatment options). Pregnancy should be avoided in women receiving efavirenz. Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives).

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. Some health experts recommend that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.
4.7 Effects on ability to drive and use machines

Efavirenz has not been specifically evaluated for possible effects on the ability to drive a car or operate machinery. 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

Efavirenz has been studied in over 2,000 patients. In a subset of 413 patients who received 600 mg efavirenz daily in combination with protease inhibitors and/or NRTIs in controlled clinical studies, the most frequently reported treatment related undesirable effects of at least moderate severity were rash (13.1%), nausea (10.4%), dizziness (9.2%), diarrhoea (6.8%), headache (6.3%), insomnia (6.1%), fatigue (5.6%) and impaired concentration (5.3%). Nausea was reported at higher frequency and diarrhoea was reported with about equal frequency in the control groups. The most notable undesirable effects associated with efavirenz are rash and nervous system symptoms (see 4.4 Special warnings and special precautions for use).

A few cases of pancreatitis have been described although causal relationship with efavirenz has not been established.

The type and frequency of undesirable effects in children was generally similar to that of adult patients with the exception that rash was reported more frequently in children and was more often of higher grade than in adults.

**Rash:** In clinical studies, 28% of patients treated with 600 mg of efavirenz experienced skin rash compared with 18% of patients treated in control groups. Skin rash was considered treatment related in 18% of patients treated with efavirenz. Severe rash occurred in 0.7% of patients treated with efavirenz and 1.7% discontinued therapy because of rash. In over 2,000 patients treated with efavirenz, the incidence of erythema multiforme or Stevens-Johnson Syndrome was 0.14%.

Rash was reported in 23 of 57 children (40%) treated with efavirenz and was severe in 4 patients (7%). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

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

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

**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. In
controlled clinical studies where 600 mg efavirenz was administered with other antiretroviral agents, 22.8% of patients experienced nervous system symptoms of moderate-to-severe intensity compared to 10.1% of patients receiving control regimens. These symptoms were severe in 2.9% of patients receiving efavirenz 600 mg daily and in 1.3% of patients receiving control regimens. Additionally psychosis-like reactions have been observed in approximately 1 – 2 per 1,000 patients treated with efavirenz. In clinical studies 2.7% of patients treated with 600 mg of efavirenz discontinued therapy because of nervous system symptoms. Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2-4 weeks. In 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. 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 4.2 Posology and method of administration). Dose reduction or splitting the daily dose has not been shown to provide benefit.

**Laboratory test abnormalities:**

**Liver enzymes:** Elevations of AST to greater than five times the upper limit of the normal range were seen in 2% of 391 patients treated with 600 mg of efavirenz and 3% of 283 patients treated with control regimens. Elevations of ALT to greater than five times the upper limit of normal were seen in 3% and 2% of patients treated with 600 mg of efavirenz and control regimens, respectively. In 53 patients treated with 600 mg of efavirenz who were seropositive for Hepatitis B and/or C, 6% developed AST levels and 13% developed ALT levels of this magnitude. In 41 patients seropositive for Hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 2% developed ALT elevations to these levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4% of all patients treated with 600 mg of efavirenz and in 11% of patients seropositive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 2%, irrespective of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity (see 4.4 Special warnings and special precautions for use).

**Lipids:** Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving efavirenz. Modest elevations of serum triglycerides and cholesterol have also been observed in patients receiving efavirenz; however the significance of these findings is unknown, in part because samples were obtained from non-fasting patients. The effect of efavirenz on total, LDL, and HDL cholesterol in patients receiving long term therapy with efavirenz has not been evaluated (see 4.4 Special warnings and special precautions for use).

**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.

**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.

LOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HIV-1 specific non-nucleoside reverse-transcriptase inhibitor (NNRTI).
ATC code: J05A G 03

Mechanism of action: Efavirenz is a non-nucleoside reverse transcriptase inhibitor (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. Substitutions at RT positions 100, 101, 108, 138, 188 or 190 were also observed, but at lower frequencies, and often only in combination with K103N. The K103N substitution was not observed in patient samples obtained prior to treatment with efavirenz. 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 protease inhibitors 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.

**Pharmacodynamic effects**

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts <50 cells/mm³, or in protease inhibitor or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited. Long term efficacy and safety studies are ongoing.

Controlled clinical studies of up to 24 weeks duration with efavirenz in combination with NRTIs and/or protease inhibitors 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. In Studies 006, 020 and ACTG 364 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.

Efficacy results 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 studies 006, 020 and ACTG 364

<table>
<thead>
<tr>
<th>Study Number/Treatment Regimens **</th>
<th>n</th>
<th>Responder rates (NC=F**)</th>
<th>Mean change from baseline-CD4 cell counts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Plasma HIV RNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 400 copies/ml</td>
<td>&lt;50 copies/ml</td>
</tr>
<tr>
<td>Study 006 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV+ZDV+3TC</td>
<td>15</td>
<td>75 ((68, 82))</td>
<td>58 (50, 66)</td>
</tr>
<tr>
<td>EFV+IDV</td>
<td>14</td>
<td>66 ((58, 73))</td>
<td>46 (38, 54)</td>
</tr>
<tr>
<td>IDV+ZDV+3TC</td>
<td>14</td>
<td>56 ((48, 64))</td>
<td>43 (35, 52)</td>
</tr>
<tr>
<td>Study 020 24 weeks</td>
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</tr>
<tr>
<td>EFV+IDV+NRTIs</td>
<td>92</td>
<td>64 ((53, 74))</td>
<td>54 (44, 65)</td>
</tr>
<tr>
<td>IDV+NRTIs</td>
<td>92</td>
<td>52 ((41, 63))</td>
<td>36 (25, 46)</td>
</tr>
<tr>
<td>Study ACTG 364 24 weeks</td>
<td></td>
<td></td>
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<tr>
<td>Regimen</td>
<td>Patients</td>
<td>Viral Load (copies/ml)</td>
<td>Min.</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>EFV+NFV+NRT</td>
<td>64</td>
<td>78</td>
<td>67, 89</td>
</tr>
<tr>
<td>EFV+NRTIs</td>
<td>65</td>
<td>60</td>
<td>48, 72</td>
</tr>
<tr>
<td>NFV+NRTIs</td>
<td>66</td>
<td>45</td>
<td>33, 58</td>
</tr>
</tbody>
</table>

* < 500 copies/ml for ACTG 364
** EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir; ---, not performed; S.E.M., standard error of the mean; NC=F, noncompleter=failure; C.I., confidence interval

Study 006 evaluated 450 patients not previously treated with protease inhibitors, NNRTIs, or lamivudine. This study was designed to test the equivalence of the regimens. The higher rate of premature discontinuations as a result of adverse experiences in the control group of this open-label study contributed to the differences in the responder rates.

Study 020 evaluated 184 patients who had been treated with NRTIs but not with protease inhibitors 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.

Study ACTG 364 evaluated 195 patients who had been treated with NRTIs but not with protease inhibitors or NNRTIs.

**Paediatric trial:** ACTG 382 is an ongoing 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 20 weeks was 61% (95%, C.I. 48, 74), and the mean CD4 cell counts were increased by 100 ± 37.5 cells/mm³ from baseline.

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 patients receiving efavirenz 600 mg once daily, mean steady state C_max was 12.9 μM, steady state C_min was 5.6 μM, and AUC was 184 μM·h.

**The effect of food:** In uninfected volunteers, meals of normal composition had no appreciable effect on bioavailability of 100 mg of efavirenz administered twice a day for 10 days with meals. The relative bioavailability of a single 1,200 mg dose of efavirenz in uninfected volunteers was increased 50% following a high fat meal.
**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 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 of 40-55 hours (single dose half-life 52-76 hours).

**Elimination:** Efavirenz has a relatively long terminal half-life of 52 to 76 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.

In the single patient studied with severe hepatic impairment (Child Pugh Grade C), half life was doubled indicating a potential for a much greater degree of accumulation.

**Paediatric pharmacokinetics:** In 48 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 14.2 μM, steady state C_{min} was 5.6 μM, and AUC was 218 μM·h. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

**Gender, race, elderly:** Pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied. Although limited data suggest that 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.

### 5.3 Preclinical safety data

Long-term carcinogenicity studies of efavirenz in rats and mice are in progress.

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 cynomolagus monkeys given doses resulting in
plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia 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.

Increases in ALT activity were observed in cynomolgous monkeys given efavirenz at doses corresponding to the exposure levels seen in humans. Minimal biliary hyperplasia was observed in four of eight cynomolgus monkeys given efavirenz for 1 year at a dose resulting in mean AUC values approximately 5 fold greater than those in humans given the recommended dose. Biliary fibrosis has been observed in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium lauryl sulphate, lactose monohydrate, magnesium stearate and sodium starch glycolate.

The capsule shell: gelatine, sodium lauryl sulphate, titanium dioxide (E171) and silicon dioxide.

Printing ink: cochineal carminic acid (E120), indigo carmine (E132), and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

18 months.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and content of container

HDPE bottles with a child-resistant polypropylene closure. Bottles of 30 hard capsules.
No special requirements.

7. MARKETING

AUTHORISATION HOLDER

DuPont Pharmaceuticals Limited
Wedgwood Way
Stevenage
Hertfordshire, SG1 4QN
United Kingdom

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT
SUSTIVA 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 200 mg efavirenz
For excipients see 6.1 List of excipients

3. PHARMACEUTICAL FORM
Hard capsule
SUSTIVA 200 mg hard capsules are 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 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 protease inhibitors has not been documented, there are at present insufficient data on the efficacy of subsequent use of protease inhibitor based combination therapy after failure of regimens containing SUSTIVA.

See 5.1 Pharmacodynamic properties: Pharmacodynamic effects for a summary of clinical and pharmacodynamic information.

4.2 Posology and method of administration
Concomitant antiretroviral therapy: SUSTIVA must be given in combination with other antiretroviral medications (see 4.5 Interactions with other medicinal products).

SUSTIVA may be taken with or without food (see 5.2 Pharmacokinetic properties: The effect of food).
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 4.8 Undesirable effects).

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

**Adults:** The recommended dosage of SUSTIVA in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily.

**Adolescents and children (3 to 17 years):** The recommended dose of SUSTIVA in combination with a protease inhibitor 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. SUSTIVA has not been studied in children under the age of 3 years or children weighing less than 13 kg.

<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>

**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 4.4 Special warnings and special precautions for use: Special populations).

**Liver disease:** Patients with mild to moderate liver disease may be treated cautiously with efavirenz, 600 mg once daily. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms (see 4.3 Contra-indications and 4.4 Special warnings and special precautions for use: Special populations).

4.3 Contra-indications

SUSTIVA is contraindicated in patients with clinically significant hypersensitivity to the active substance or to any of the excipients.

Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Grade C) (see 5.2 Pharmacokinetic properties).

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, or triazolam because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening...
undesirable effects [e.g., cardiac arrhythmias, prolonged sedation or respiratory depression] (see 4.5 Interactions with other medicinal products).

4.4 Special warnings and special 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. Therapy with efavirenz must always be initiated in combination with one or more new antiretroviral agent(s) to which the patient has not been previously exposed. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance. Resistant virus emerges rapidly when efavirenz is administered as monotherapy.

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 medication in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medications. The antiretroviral medications 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.

Skin 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 0.14%. 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 anti-retroviral agents to avoid development of resistant virus (see 4.8 Undesirable effects).

Rash was reported in 23 of 57 children (40%) treated with SUSTIVA and was severe in four patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Patients who discontinued treatment with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) due to rash may be at higher risk of developing rash during treatment with efavirenz.

Nervous system symptoms: Nervous system symptoms have been reported in clinical studies with efavirenz (see 4.8 Undesirable effects). In addition, there have been reports (approximately 1-2 per thousand patients treated with efavirenz) of psychosis-like reactions, such as delusions and inappropriate behaviour, predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both efavirenz-treated and control-treated patients, particularly in patients with a previous history of depression. Patients
should be advised that if they experience these symptoms they should contact their doctor immediately because discontinuation of efavirenz may be required.

**Special populations:** Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild-to-moderate liver disease. A 600 mg dose once daily is recommended. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see 4.2 Posology and method of administration).

In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with 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 unknown risks of significant liver toxicity (see 4.8 Undesirable effects).

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 4.2 Posology and method of administration). There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

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

Efavirenz has not been evaluated in children below 3 years of age or who weigh less than 13 kg.

**Cholesterol:** Monitoring of cholesterol should be considered in patients treated with efavirenz (see 4.8 Undesirable effects).

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

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

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, or triazolam (see 4.3 Contraindications).

**Concomitant antiretroviral agents**

**Nelfinavir:** The AUC and $C_{\text{max}}$ of nelfinavir are increased by 20% and 21%, respectively when given with efavirenz. The combination was generally well tolerated and no dose adjustment is necessary when nelfinavir is administered in combination with efavirenz.
Indinavir: When indinavir (800 mg every 8 hours) was given with efavirenz (200 mg every 24 hours), the indinavir AUC and C\text{max} were decreased by approximately 31% and 16%, respectively, as a result of enzyme induction. The degree of reduction in indinavir levels may be greater when efavirenz 600 mg every 24 hours is given. Higher doses of indinavir offset the metabolic induction by efavirenz. At present the recommendation is to increase the dose of indinavir from 800 mg every 8 hours to 1,000 mg every 8 hours when efavirenz and indinavir are co-administered. No adjustment of the dose of efavirenz is necessary when given with indinavir.

Ritonavir: When efavirenz 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) were studied in uninfected volunteers the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.

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

Saquinavir/ritonavir: No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir.

Nucleoside analogue reverse transcriptase inhibitors (NRTIs): Studies of the interaction between efavirenz and the combination of zidovudine and lamivudine were performed in HIV infected patients. No clinically significant pharmacokinetic interactions were observed. Specific interaction studies have not been performed with efavirenz and other NRTIs. Clinically significant interactions would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): No studies have been performed with efavirenz in combination with other non-nucleoside reverse transcriptase inhibitors and the potential for pharmacokinetic or pharmacodynamic interactions is unknown.

Antimicrobial agents:

Rifamycins: Rifampicin reduced efavirenz AUC by 26% and C\text{max} by 20% in uninfected volunteers. The dose of efavirenz must be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with efavirenz. Rifabutin has not been studied in combination with efavirenz.

Macrolide antibiotics:

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

Clarithromycin: Co-administration of 400 mg of efavirenz once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C\text{max} of clarithromycin decreased 39% and 26%, respectively, while the AUC and C\text{max} of the active clarithromycin
hydroxymetabolite were increased 34% and 49%, respectively, when used in combination with efavirenz. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin should be considered.

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

**Antifungal agents:**

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

**Other interactions**

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

**Oral contraceptives:** Only the ethinyloestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinyloestradiol was increased (37%) by efavirenz. No significant changes were observed in C\text{max} of ethinyloestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyloestradiol on efavirenz C\text{max} or AUC was observed. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

**Phenytoin and phenobarbital:** No data are available on the potential interactions of efavirenz with phenytoin or phenobarbital. When efavirenz is administered concomitantly with phenytoin or phenobarbital there is the potential for reduction in the plasma concentrations of each agent.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available for efavirenz. Studies in animals have shown reproductive toxicity including marked teratogenic effects (see 5.3 Preclinical safety data). Therefore, efavirenz should not be used during pregnancy unless clearly necessary (the potential benefit to the mother outweighs the potential risk to the foetus and there are no other appropriate treatment options). Pregnancy should be avoided in women receiving efavirenz. Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives).

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 breastfeed their infants. Some health experts recommend that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.
4.7 Effects on ability to drive and use machines

Efavirenz has not been specifically evaluated for possible effects on the ability to drive a car or operate machinery. 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

Efavirenz has been studied in over 2,000 patients. In a subset of 413 patients who received 600 mg efavirenz daily in combination with protease inhibitors and/or NRTIs in controlled clinical studies, the most frequently reported treatment related undesirable effects of at least moderate severity were rash (13.1%), nausea (10.4%), dizziness (9.2%), diarrhoea (6.8%), headache (6.3%), insomnia (6.1%), fatigue (5.6%) and impaired concentration (5.3%). Nausea was reported at higher frequency and diarrhoea was reported with about equal frequency in the control groups. The most notable undesirable effects associated with efavirenz are rash and nervous system symptoms (see 4.4 Special warnings and special precautions for use).

A few cases of pancreatitis have been described although causal relationship with efavirenz has not been established.

The type and frequency of undesirable effects in children was generally similar to that of adult patients with the exception that rash was reported more frequently in children and was more often of higher grade than in adults.

Rash: In clinical studies, 28% of patients treated with 600 mg of efavirenz experienced skin rash compared with 18% of patients treated in control groups. Skin rash was considered treatment related in 18% of patients treated with efavirenz. Severe rash occurred in 0.7% of patients treated with efavirenz and 1.7% discontinued therapy because of rash. In over 2,000 patients treated with efavirenz, the incidence of erythema multiforme or Stevens-Johnson Syndrome was 0.14%.

Rash was reported in 23 of 57 children (40%) treated with efavirenz and was severe in 4 patients (7%). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

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

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

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. In
controlled clinical studies where 600 mg efavirenz was administered with other antiretroviral agents, 22.8% of patients experienced nervous system symptoms of moderate-to-severe intensity compared to 10.1% of patients receiving control regimens. These symptoms were severe in 2.9% of patients receiving efavirenz 600 mg daily and in 1.3% of patients receiving control regimens. Additionally, psychosis-like reactions have been observed in approximately 1 – 2 per 1,000 patients treated with efavirenz. In clinical studies 2.7% of patients treated with 600 mg of efavirenz discontinued therapy because of nervous system symptoms. Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2-4 weeks. In 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. 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 4.2 Posology and method of administration). Dose reduction or splitting the daily dose has not been shown to provide benefit.

**Laboratory test abnormalities:**

**Liver enzymes:** Elevations of AST to greater than five times the upper limit of the normal range were seen in 2% of 391 patients treated with 600 mg of efavirenz and 3% of 283 patients treated with control regimens. Elevations of ALT to greater than five times the upper limit of normal were seen in 3% and 2% of patients treated with 600 mg of efavirenz and control regimens, respectively. In 53 patients treated with 600 mg of efavirenz who were seropositive for Hepatitis B and/or C, 6% developed AST levels and 13% developed ALT levels of this magnitude. In 41 patients seropositive for Hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 2% developed ALT elevations to these levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4% of all patients treated with 600 mg of efavirenz and in 11% of patients seropositive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 2%, irrespective of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity (see 4.4 Special warnings and special precautions for use).

**Lipids:** Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving efavirenz. Modest elevations of serum triglycerides and cholesterol have also been observed in patients receiving efavirenz; however, the significance of these findings is unknown, in part because samples were obtained from non-fasting patients. The effect of efavirenz on total, LDL, and HDL cholesterol in patients receiving long-term therapy with efavirenz has not been evaluated (see 4.4 Special warnings and special precautions for use).

**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.

**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.

LOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HIV-1 specific non-nucleoside reverse-transcriptase inhibitor (NNRTI).
ATC code: J05A G 03

Mechanism of action: Efavirenz is a non-nucleoside reverse transcriptase inhibitor (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. Substitutions at RT positions 100, 101, 108, 138, 188 or 190 were also observed, but at lower frequencies, and often only in combination with K103N. The K103N substitution was not observed in patient samples obtained prior to treatment with efavirenz. 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 protease inhibitors 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.

**Pharmacodynamic effects**

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts <50 cells/mm$^3$, or in protease inhibitor or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited. Long term efficacy and safety studies are ongoing.

Controlled clinical studies of up to 24 weeks duration with efavirenz in combination with NRTIs and/or protease inhibitors 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. In Studies 006, 020 and ACTG 364 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.

Efficacy results 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 studies 006, 020 and ACTG 364

<table>
<thead>
<tr>
<th>Study Number/Treatment Regimens **</th>
<th>n</th>
<th>Plasma HIV RNA</th>
<th>Mean change from baseline-CD4 cell counts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 400 copies/ml</td>
<td>&lt;50 copies/ml</td>
</tr>
<tr>
<td>Study 006 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EFV+ZDV+3TC</strong></td>
<td>15</td>
<td>75</td>
<td>58</td>
</tr>
<tr>
<td><strong>EFV+IDV</strong></td>
<td>14</td>
<td>66</td>
<td>46</td>
</tr>
<tr>
<td><strong>IDV+ZDV+3TC</strong></td>
<td>14</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>Study 020 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EFV+IDV+NRTIs</strong></td>
<td>92</td>
<td>64</td>
<td>54</td>
</tr>
<tr>
<td><strong>IDV+NRTIs</strong></td>
<td>92</td>
<td>52</td>
<td>36</td>
</tr>
<tr>
<td>Study ACTG 364 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study 006 evaluated 450 patients not previously treated with protease inhibitors, NNRTIs, or lamivudine. This study was designed to test the equivalence of the regimens. The higher rate of premature discontinuations as a result of adverse experiences in the control group of this open-label study contributed to the differences in the responder rates.

Study 020 evaluated 184 patients who had been treated with NRTIs but not with protease inhibitors 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.

Study ACTG 364 evaluated 195 patients who had been treated with NRTIs but not with protease inhibitors or NNRTIs.

**Paediatric trial:** ACTG 382 is an ongoing 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 20 weeks was 61% (95%, C.I. 48, 74), and the mean CD4 cell counts were increased by 100 ± 37.5 cells/mm³ from baseline.

### 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 patients receiving efavirenz 600 mg once daily, mean steady state C<sub>max</sub> was 12.9 μM, steady state C<sub>min</sub> was 5.6 μM, and AUC was 184 μM·h.

**The effect of food:** In uninfected volunteers, meals of normal composition had no appreciable effect on bioavailability of 100 mg of efavirenz administered twice a day for 10 days with meals. The relative bioavailability of a single 1,200 mg dose of efavirenz in uninfected volunteers was increased 50% following a high fat meal.
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 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 of 40-55 hours (single dose half-life 52-76 hours).

Elimination: Efavirenz has a relatively long terminal half-life of 52 to 76 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.

In the single patient studied with severe hepatic impairment (Child Pugh Grade C), half life was doubled indicating a potential for a much greater degree of accumulation.

Paediatric pharmacokinetics: In 48 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 14.2 $\mu$M, steady state $C_{\text{min}}$ was 5.6 $\mu$M, and AUC was 218 $\mu$M·h. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

Gender, race, elderly: Pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied. Although limited data suggest that 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.

5.3 Preclinical safety data

Long-term carcinogenicity studies of efavirenz in rats and mice are in progress.

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 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.

Increases in ALT activity were observed in cynomolgus monkeys given efavirenz at doses corresponding to the exposure levels seen in humans. Minimal biliary hyperplasia was observed in four of eight cynomolgus monkeys given efavirenz for 1 year at a dose resulting in mean AUC values approximately 5 fold greater than those in humans given the recommended dose. Biliary fibrosis has been observed in rats.

6.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium lauryl sulphate, lactose monohydrate, magnesium stearate and sodium starch glycolate.

The capsule shell: gelatine, sodium lauryl sulphate, yellow iron oxide (E172), and silicon dioxide.

Printing ink: cochineal carminic acid (E120), indigo carmine (E132), and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

18 months.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and content of container


6.6 Instructions for use and handling
No special requirements.

7. AUTHORISATION HOLDER

DuPont Pharmaceuticals Limited
Wedgwood Way
Stevenage
Hertfordshire, SG1 4QN
United Kingdom

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
A. MANUFACTURING AUTHORISATION HOLDER

Manufacturer responsible for batch release in the European Economic Area

DuPont Pharma GmbH, DuPont Strasse 1, Bad Homburg, D-61352 Germany.

Manufacturing authorisation issued on 21 August 1997 by Regierungspräsidium Darmstadt, Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

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


4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use  
Read the enclosed 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: {month/year}

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**

DuPont Pharmaceuticals Limited  
Wedgwood Way  
Stevenage  
Hertfordshire SG1 4QN  
United Kingdom

12. **NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

EU/0/00/000/000

13. **MANUFACTURER’S BATCH NUMBER**

Lot: {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

15. **INSTRUCTIONS ON USE**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

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

Each hard capsule contains: colouring agents E120, E132, E171 and other excipients.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use
Read the enclosed 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: {month/year}

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**

DuPont Pharmaceuticals Limited  
Wedgwood Way  
Stevenage  
Hertfordshire SG1 4QN  
United Kingdom

12. **NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

EU/0/00/000/000

13. **MANUFACTURER’S BATCH NUMBER**

Lot: {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

15. **INSTRUCTIONS ON USE**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

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


4. PHARMACEUTICAL FORM AND CONTENTS

90 hard capsules

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use
Read the enclosed 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: {month/year}

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

DuPont Pharmaceuticals Limited
Wedgwood Way
Stevenage
Hertfordshire SG1 4QN
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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**


4. **PHARMACEUTICAL FORM AND CONTENTS**

42 hard capsules

5. **METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION**

Oral use
Read the enclosed 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: {month/year}

9. **SPECIAL STORAGE CONDITIONS**

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

56
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

DuPont Pharmaceuticals Limited
Wedgwood Way
Stevenage
Hertfordshire SG1 4QN
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1.  **NAME OF THE MEDICINAL PRODUCT**

Sustiva 200 mg hard capsules
efavirenz

2.  **NAME OF THE MARKETING AUTHORISATION HOLDER**

DuPont Pharmaceuticals Limited

3.  **EXPIRY DATE**

Exp:  {month/year}

4.  **BATCH NUMBER**

Lot:  {number}
B. PACKAGE LEAFLET
PACKAGE LEAFLET

SUSTIVA 50 mg hard capsules (efavirenz)

Please read this leaflet carefully before you start to take your medicine. Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else. Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your pharmacist.

What is SUSTIVA?

- Each SUSTIVA hard capsule contains 50 mg of efavirenz as the active substance.
- SUSTIVA 50 mg hard capsules also contain the following other ingredients: sodium lauryl sulphate, lactose monohydrate, magnesium stearate and sodium starch glycolate. The capsule shell contains as excipients: gelatine, sodium lauryl sulphate, 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).
- SUSTIVA 50 mg capsules are supplied in bottles of 30 capsules.
- SUSTIVA belongs to a class of antiretroviral medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). It is an antiretroviral medicine that fights HIV infection by reducing the amount of virus in blood.

Marketing Authorisation Holder

DuPont Pharmaceuticals Ltd
Wedgwood Way
Stevenage
Hertfordshire, SG1 4QN
United Kingdom

Manufacturer

DuPont Pharma GmbH
DuPont Strasse 1
D-61352 Bad Homburg
Germany

Why has my doctor prescribed SUSTIVA?

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.

Who should not take SUSTIVA?

Do not take SUSTIVA if you know you are allergic to any of the ingredients in SUSTIVA hard capsules. SUSTIVA should not be taken with some other medicines that are listed below.

Medicines that cannot be taken with SUSTIVA include astemizole, cisapride, terfenadine, midazolam, and triazolam. Taking these medicines with SUSTIVA could create the potential for serious and/or life-threatening side-effects.

You should not take SUSTIVA if you have severe liver disease.

What are the appropriate precautions for use?

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 multiplying, another
medicine you have not taken before must be started at the same time. (See Can I take SUSTIVA with other medicines?).

You should know that SUSTIVA is not a cure for HIV infection and that 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.

Treatment with SUSTIVA has not been shown to reduce the risk of passing on HIV infection to others through sexual contact or blood contamination.

**What should I tell my doctor before I take SUSTIVA?**

Inform your doctor about any past or present medical problems, including liver disease (such as hepatitis B or C), allergies, mental illness, substance or alcohol abuse. Also inform your doctor about any medications, vitamins, or nutritional supplements that you are currently taking, have taken recently or intend to take.

**Can SUSTIVA be taken by children?**

SUSTIVA can be taken by children 3 years of age and older who are able to swallow the hard capsules (see below how SUSTIVA should be taken).

**What should I consider concerning contraception, pregnancy, or breast-feeding?**

Inform your doctor 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.

Malformations have been seen in foetuses from animals treated with SUSTIVA; therefore, pregnancy should be avoided in women receiving SUSTIVA. A reliable form of barrier contraception (for example a condom) should always be used with other methods of contraception including oral (pill) or other hormonal contraceptives (e.g., implants, injection).

You should not breast feed your baby if you are taking SUSTIVA.

**Can I take SUSTIVA with other medicines?**

Medicines that cannot be taken with SUSTIVA include astemizole, cisapride, terfenadine, midazolam, and triazolam. Taking these medicines with SUSTIVA could create the potential for serious and/or life-threatening side-effects.

SUSTIVA may be taken with many of the medicines commonly used in people with HIV infection. These include the protease inhibitors, (e.g., nelfinavir and indinavir) and nucleoside analogue reverse transcriptase inhibitors (NRTIs). The dose of indinavir must be increased when taken with SUSTIVA. Use of SUSTIVA with saquinavir alone is not recommended.

If you are taking the antibiotic clarithromycin, your doctor may consider giving you an alternative antibiotic. If you are taking rifampicin, your doctor will prescribe a higher dose of SUSTIVA.

You should always inform your doctor about all medicines you are taking, have recently taken or plan to take, including those obtained without a prescription.
Can I drive or operate machinery while I am taking SUSTIVA?

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

How should SUSTIVA be taken?

SUSTIVA hard capsules may be taken with or without food.

- The dose for adults, and 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>

Your doctor will give you instructions for proper dosage.

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 medications.

It is important that you take SUSTIVA exactly as your doctor prescribes. You should not stop taking it without first consulting your doctor.

What should I do if I take too much?

If you take too much SUSTIVA consult your doctor or hospital.

What should I do if I miss a dose?

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

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.

What undesirable effects may SUSTIVA have?

Any medicine may have unintended or undesirable effects, so-called side effects. The most frequently reported adverse reactions associated with SUSTIVA in combination with other anti-HIV medications include rash, nausea, dizziness, diarrhoea, headache, insomnia (difficulty sleeping), fatigue, and impaired concentration.
The most notable unwanted effects are skin rash and nervous system symptoms that include dizziness, insomnia, somnolence (drowsiness), impaired concentration, and abnormal dreaming.

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. If you are affected your doctor may suggest that you take SUSTIVA at bedtime. Rarely, some patients have more serious symptoms that may affect mood or the ability to think clearly. Always notify your doctor immediately if you have these symptoms or any side effects while taking SUSTIVA.

Other side effects may occur with SUSTIVA. Your doctor or pharmacist has a more complete list of side effects. Inform your doctor promptly about these or any other undesirable effects, especially if not mentioned in this leaflet. If the condition persists or worsens, seek medical attention.

How long can I keep my medicine?

Do not use this medicine after the month and year shown by the numbers following expiry date on the container.

How should I store SUSTIVA?

There are no special storage instructions.

Keep out of the reach and sight of children.

This package leaflet was last revised
OTHER INFORMATION

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

Belgique/België/Belgien
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64
SUSTIVA 100 mg hard capsules (efavirenz)

Please read this leaflet carefully before you start to take your medicine. Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else. Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your pharmacist.

What is SUSTIVA?

- Each SUSTIVA hard capsule contains 100 mg of efavirenz as the active substance.
- SUSTIVA 100 mg hard capsules also contain the following other ingredients: sodium lauryl sulphate, lactose monohydrate, magnesium stearate and sodium starch glycolate. The capsule shell contains as excipients: gelatine, sodium lauryl sulphate, titanium dioxide (E171) and silicon dioxide. The capsules are printed with inks containing cochineal carminic acid (E120), indigo carmine (E132), and titanium dioxide (E171).
- SUSTIVA 100 mg capsules are supplied in bottles of 30 capsules.
- SUSTIVA belongs to a class of antiretroviral medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). It is an antiretroviral medicine that fights HIV infection by reducing the amount of virus in blood.

Why has my doctor prescribed SUSTIVA?

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.

Who should not take SUSTIVA?

Do not take SUSTIVA if you know you are allergic to any of the ingredients in SUSTIVA hard capsules. SUSTIVA should not be taken with some other medicines that are listed below.

Medicines that cannot be taken with SUSTIVA include astemizole, cisapride, terfenadine, midazolam, and triazolam. Taking these medicines with SUSTIVA could create the potential for serious and/or life-threatening side-effects.

You should not take SUSTIVA if you have severe liver disease.
What are the appropriate precautions for use?

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 multiplying, another medicine you have not taken before must be started at the same time. (See Can I take SUSTIVA with other medicines?).

You should know that SUSTIVA is not a cure for HIV infection and that 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.

Treatment with SUSTIVA has not been shown to reduce the risk of passing on HIV infection to others through sexual contact or blood contamination.

What should I tell my doctor before I take SUSTIVA?

Inform your doctor about any past or present medical problems, including liver disease (such as hepatitis B or C), allergies, mental illness, substance or alcohol abuse. Also inform your doctor about any medications, vitamins, or nutritional supplements that you are currently taking, have taken recently or intend to take.

Can SUSTIVA be taken by children?

SUSTIVA can be taken by children 3 years of age and older who are able to swallow the hard capsules (see below how SUSTIVA should be taken).

What should I consider concerning contraception, pregnancy, or breast-feeding?

Inform your doctor 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.

Malformations have been seen in foetuses from animals treated with SUSTIVA; therefore, pregnancy should be avoided in women receiving SUSTIVA. A reliable form of barrier contraception (for example a condom) should always be used with other methods of contraception including oral (pill) or other hormonal contraceptives (e.g., implants, injection).

You should not breast feed your baby if you are taking SUSTIVA.

Can I take SUSTIVA with other medicines?

Medicines that cannot be taken with SUSTIVA include astemizole, cisapride, terfenadine, midazolam, and triazolam. Taking these medicines with SUSTIVA could create the potential for serious and/or life-threatening side-effects.

SUSTIVA may be taken with many of the medicines commonly used in people with HIV infection. These include the protease inhibitors, (e.g., nelfinavir and indinavir) and nucleoside analogue reverse transcriptase inhibitors (NRTIs). The dose of indinavir must be increased when taken with SUSTIVA. Use of SUSTIVA with saquinavir alone is not recommended.

If you are taking the antibiotic clarithromycin, your doctor may consider giving you an alternative antibiotic. If you are taking rifampicin, your doctor will prescribe a higher dose of SUSTIVA.
You should always inform your doctor about all medicines you are taking, have recently taken or plan to take, including those obtained without a prescription.

**Can I drive or operate machinery while I am taking SUSTIVA?**

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

**How should SUSTIVA be taken?**

SUSTIVA hard capsules may be taken with or without food.

- The dose for adults, and 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>
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<tr>
<td>15 to &lt; 20</td>
<td>250</td>
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<td>20 to &lt; 25</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>
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</tr>
</tbody>
</table>

Your doctor will give you instructions for proper dosage.

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 medications.

It is important that you take SUSTIVA exactly as your doctor prescribes. You should not stop taking it without first consulting your doctor.

**What should I do if I take too much?**

If you take too much SUSTIVA consult your doctor or hospital.

**What should I do if I miss a dose?**

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

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.
What undesirable effects may SUSTIVA have?

Any medicine may have unintended or undesirable effects, so-called side effects. The most frequently reported adverse reactions associated with SUSTIVA in combination with other anti-HIV medications include rash, nausea, dizziness, diarrhoea, headache, insomnia (difficulty sleeping), fatigue, and impaired concentration.

The most notable unwanted effects are skin rash and nervous system symptoms that include dizziness, insomnia, somnolence (drowsiness), impaired concentration, and abnormal dreaming.

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. If you are affected your doctor may suggest that you take SUSTIVA at bedtime. Rarely, some patients have more serious symptoms that may affect mood or the ability to think clearly. Always notify your doctor immediately if you have these symptoms or any side effects while taking SUSTIVA.

Other side effects may occur with SUSTIVA. Your doctor or pharmacist has a more complete list of side effects. Inform your doctor promptly about these or any other undesirable effects, especially if not mentioned in this leaflet. If the condition persists or worsens, seek medical attention.

How long can I keep my medicine?

Do not use this medicine after the month and year shown by the numbers following expiry date on the container.

How should I store SUSTIVA?

There are no special storage instructions.

Keep out of the reach and sight of children.

This package leaflet was last revised
OTHER INFORMATION

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

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Italia
PACKAGE LEAFLET

SUSTIVA 200 mg hard capsules (efavirenz)

Please read this leaflet carefully before you start to take your medicine. Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else. Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your pharmacist.

What is SUSTIVA?

- Each SUSTIVA hard capsule contains 200 mg of efavirenz as the active substance.
- SUSTIVA 200 mg hard capsules also contain the following other ingredients: sodium lauryl sulphate, lactose monohydrate, magnesium stearate and sodium starch glycolate. The capsule shell contains as excipients: gelatine, sodium lauryl sulphate, 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).
- SUSTIVA 200 mg capsules are supplied in bottles of 90 capsules and in blister packs containing 42 capsules.
- SUSTIVA belongs to a class of antiretroviral medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). It is an antiretroviral medicine that fights HIV infection by reducing the amount of virus in blood.

Marketing Authorisation Holder

DuPont Pharmaceuticals Ltd
Wedgwood Way
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United Kingdom

Manufacturer

DuPont Pharma GmbH
DuPont Strasse 1
D-61352 Bad Homburg
Germany

Why has my doctor prescribed SUSTIVA?

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.

Who should not take SUSTIVA?

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