

1 **SUSTIVA[®]**
2 **(efavirenz) capsules and tablets**

3 **Rx only**

4 **DESCRIPTION**

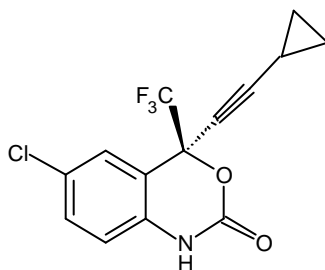
5 SUSTIVA[®] (efavirenz) is a human immunodeficiency virus type 1 (HIV-1) specific, non-
6 nucleoside, reverse transcriptase inhibitor (NNRTI).

7 **Capsules:** SUSTIVA is available as capsules for oral administration containing either
8 50 mg, 100 mg, or 200 mg of efavirenz and the following inactive ingredients: lactose
9 monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycolate.
10 The capsule shell contains the following inactive ingredients and dyes: gelatin, sodium
11 lauryl sulfate, titanium dioxide, and/or yellow iron oxide. The capsule shells may also
12 contain silicon dioxide. The capsules are printed with ink containing carmine 40 blue,
13 FD&C Blue No. 2, and titanium dioxide.

14 **Tablets:** SUSTIVA is available as film-coated tablets for oral administration containing
15 600 mg of efavirenz and the following inactive ingredients: croscarmellose sodium,
16 hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline
17 cellulose, and sodium lauryl sulfate. The film coating contains Opadry[®] Yellow and
18 Opadry[®] Clear. The tablets are polished with carnauba wax and printed with purple ink,
19 Opacode[®] WB.

20 Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-
21 dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

22 Its empirical formula is C₁₄H₉ClF₃NO₂ and its structural formula is:



23

Opadry[®] and Opacode[®] are registered trademarks of BPSI.

24 Efavirenz is a white to slightly pink crystalline powder with a molecular mass of
25 315.68. It is practically insoluble in water (<10 µg/mL).

26 MICROBIOLOGY

27 **Mechanism of Action:** Efavirenz is a non-nucleoside reverse transcriptase (RT)
28 inhibitor of human immunodeficiency virus type 1 (HIV-1). Efavirenz activity is
29 mediated predominantly by noncompetitive inhibition of HIV-1 RT. HIV-2 RT and
30 human cellular DNA polymerases alpha, beta, gamma, and delta are not inhibited by
31 efavirenz.

32 ***In vitro* HIV Susceptibility:** The clinical significance of *in vitro* susceptibility of
33 HIV-1 to efavirenz has not been established. The *in vitro* antiviral activity of efavirenz
34 was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs),
35 and macrophage/monocyte cultures. The 90-95% inhibitory concentration (IC₉₀₋₉₅) of
36 efavirenz for wild-type laboratory adapted strains and clinical isolates ranged from 1.7 to
37 25 nM. Efavirenz demonstrated synergistic activity against HIV-1 in cell culture when
38 combined with zidovudine (ZDV), didanosine, or indinavir (IDV).

39 **Resistance:** HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold
40 increase in IC₉₀) compared to baseline can emerge *in vitro*. Phenotypic (n=26) changes in
41 evaluable HIV-1 isolates and genotypic (n=104) changes in plasma virus from selected
42 patients treated with efavirenz in combination with IDV, or with ZDV plus lamivudine
43 were monitored. One or more RT mutations at amino acid positions 98, 100, 101, 103,
44 106, 108, 188, 190, and 225, were observed in 102 of 104 patients with a frequency of at
45 least 9% compared to baseline. The mutation at RT amino acid position 103 (lysine to
46 asparagine) was the most frequently observed (≥90%). A mean loss in susceptibility
47 (IC₉₀) to efavirenz of 47-fold was observed in 26 clinical isolates. Five clinical isolates
48 were evaluated for both genotypic and phenotypic changes from baseline. Decreases in
49 efavirenz susceptibility (range from 9 to >312-fold increase in IC₉₀) were observed for
50 these isolates *in vitro* compared to baseline. All five isolates possessed at least one of the
51 efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic
52 changes associated with efavirenz therapy is under evaluation.

53 **Cross-Resistance:** Rapid emergence of HIV-1 strains that are cross-resistant to non-
54 nucleoside RT inhibitors has been observed *in vitro*. Thirteen clinical isolates previously
55 characterized as efavirenz-resistant were also phenotypically resistant to nevirapine and
56 delavirdine *in vitro* compared to baseline. Clinically derived ZDV-resistant HIV-1

57 isolates tested *in vitro* retained susceptibility to efavirenz. Cross-resistance between
58 efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets
59 involved.

60 **CLINICAL PHARMACOLOGY**

61 **Pharmacokinetics**

62 **Absorption:** Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by
63 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected
64 volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg;
65 the increases were less than proportional suggesting diminished absorption at higher
66 doses.

67 In HIV-infected patients at steady state, mean C_{max} , mean C_{min} , and mean AUC
68 were dose proportional following 200-mg, 400-mg, and 600-mg daily doses. Time-to-
69 peak plasma concentrations were approximately 3-5 hours and steady-state plasma
70 concentrations were reached in 6-10 days. In 35 patients receiving SUSTIVA 600 mg
71 once daily, steady-state C_{max} was $12.9 \pm 3.7 \mu\text{M}$ (mean \pm SD), steady-state C_{min} was $5.6 \pm$
72 $3.2 \mu\text{M}$, and AUC was $184 \pm 73 \mu\text{M}\cdot\text{h}$.

73 **Effect of Food on Oral Absorption:**

74 *Capsules*—Administration of a single 600-mg dose of efavirenz capsules with a high-
75 fat/high-caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced-fat/normal-
76 caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase
77 of 22% and 17% in efavirenz AUC_{∞} and a mean increase of 39% and 51% in efavirenz
78 C_{max} , respectively, relative to the exposures achieved when given under fasted
79 conditions. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS:**
80 **Information for Patients**.)

81 *Tablets*—Administration of a single 600-mg efavirenz tablet with a high-fat/high-caloric
82 meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28%
83 increase in mean AUC_{∞} of efavirenz and a 79% increase in mean C_{max} of efavirenz
84 relative to the exposures achieved under fasted conditions. (See **DOSAGE AND**
85 **ADMINISTRATION** and **PRECAUTIONS: Information for Patients**.)

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

92 **Metabolism:** Studies in humans and *in vitro* studies using human liver microsomes have
93 demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to
94 hydroxylated metabolites with subsequent glucuronidation of these hydroxylated
95 metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies
96 suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz
97 metabolism.

98 Efavirenz has been shown to induce P450 enzymes, resulting in the induction of
99 its own metabolism. Multiple doses of 200-400 mg per day for 10 days resulted in a
100 lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half-
101 life of 40-55 hours (single dose half-life 52-76 hours).

102 **Elimination:** Efavirenz has a terminal half-life of 52-76 hours after single doses and
103 40-55 hours after multiple doses. A one-month mass balance/excretion study was
104 conducted using 400 mg per day with a ¹⁴C-labeled dose administered on Day 8.
105 Approximately 14-34% of the radiolabel was recovered in the urine and 16-61% was
106 recovered in the feces. Nearly all of the urinary excretion of the radiolabeled drug was in
107 the form of metabolites. Efavirenz accounted for the majority of the total radioactivity
108 measured in feces.

109 **Special Populations**

110 **Hepatic Impairment:** The pharmacokinetics of efavirenz have not been adequately
111 studied in patients with hepatic impairment (see **PRECAUTIONS: General**).

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

116 **Gender and Race:** The pharmacokinetics of efavirenz in patients appear to be similar
117 between men and women and among the racial groups studied.

118 **Geriatric:** see **PRECAUTIONS: Geriatric Use**

119 **Pediatrics:** see **PRECAUTIONS: Pediatric Use**

120 **Drug Interactions (see also CONTRAINDICATIONS and**
121 **PRECAUTIONS: Drug Interactions)**

122 Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the
123 biotransformation of some drugs metabolized by CYP3A4. *In vitro* studies have shown
124 that efavirenz inhibited P450 isozymes 2C9, 2C19, and 3A4 with K_i values (8.5-17 μM)
125 in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz
126 did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82-160 μM) only
127 at concentrations well above those achieved clinically. The effects on CYP3A4 activity
128 are expected to be similar between 200-mg, 400-mg, and 600-mg doses of efavirenz.
129 Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A4
130 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs
131 which induce CYP3A4 activity would be expected to increase the clearance of efavirenz
132 resulting in lowered plasma concentrations.

133 Drug interaction studies were performed with efavirenz and other drugs likely to
134 be coadministered or drugs commonly used as probes for pharmacokinetic interaction.
135 The effects of coadministration of efavirenz on the AUC and C_{max} are summarized in
136 Table 1 (effect of efavirenz on other drugs) and Table 2 (effect of other drugs on
137 efavirenz). For information regarding clinical recommendations see **PRECAUTIONS:**
138 **Drug Interactions.**

Table 1: Effect of Efavirenz on Coadministered Drug Plasma C_{max} and AUC

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (% change)	
				C _{max} (mean [90% CI])	AUC (mean [90% CI])
Indinavir	1000 mg q8h x 10 days	600 mg x 10 days	20		
	After morning dose			↔ ^a	↓ (33%) ^a [26-39%]
	After afternoon dose			↔ ^a	↓ (37%) ^a [26-46%]
	After evening dose			↓ (29%) ^a [11-43%]	↓ (46%) ^a [37-54%]
Lopinavir/ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,7 ^b	↔ ^c	↓ (19%) ^c [↓ 36-↑ 3%]
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↑ (21%) [10-33%]	↑ (20%) [8-34%]
				Metabolite AG-1402	↓ (40%) [30-48%]
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	11		
	After AM dose			↑ (24%) [12-38%]	↑ (18%) [6-33%]
	After PM dose			↔	↔
Saquinavir SGC ^d	1200 mg q8h x 10 days	600 mg x 10 days	12	↓ (50%) [28-66%]	↓ (62%) [45-74%]
Lamivudine	150 mg q12h x 14 days	600 mg x 14 days	9	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg x 14 days	9	↔	↔
Azithromycin	600 mg single dose	400 mg x 7 days	14	↑ (22%) [4-42%]	↔
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	11	↓ (26%) [15-35%]	↓ (39%) [30-46%]
				14-OH metabolite	↑ (49%) [32-69%]
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	9	↓ (32%) [15-46%]	↓ (38%) [28-47%]
Cetirizine	10 mg single dose	600 mg x 10 days	11	↓ (24%) [18-30%]	↔
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↑ (37%) [25-51%]
Lorazepam	2 mg single dose	600 mg x 10 days	12	↑ (16%) [2-32%]	↑ (7%) [1-14%]

Table 1: Effect of Efavirenz on Coadministered Drug Plasma C_{max} and AUC

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (% change)	
				C _{max} (mean [90% CI])	AUC (mean [90% CI])
Methadone	Stable maintenance 35-100 mg daily	600 mg x 14-21 days	11	↓ 45% [25-59%]	↓ (52%) [33-66%]
Paroxetine	20 mg qd x 14 days	600 mg x 14 days	16	↔	↔
Sertraline	50 mg qd x 14 days	600 mg x 14 days	13	↓ (29%) [15-40%]	↓ (39%) [27-50%]

139 ↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change

140 ^a Comparator dose of indinavir was 800 mg q8h x 10 days. Mean decreases in the C_{min} of indinavir ranged
141 from 39 to 57%.

142 ^b Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.

143 ^c C_{min} of lopinavir was significantly decreased by 39%. The pharmacokinetics of ritonavir 100 mg q12h
144 are unaffected by concurrent efavirenz.

145 ^d Soft Gelatin Capsule.

Table 2: Effect of Coadministered Drug on Efavirenz Plasma C_{max} and AUC

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (% change)	
				C _{max} (mean [90% CI])	AUC (mean [90% CI])
Indinavir	800 mg q8h x 14 days	200 mg x 14 days	11	↔	↔
Lopinavir/ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,12 ^a	↔	↓ (16%) [↓ 38-↑ 15%]
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↔	↔
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	9	↑ (14%) [4-26%]	↑ (21%) [10-34%]
Saquinavir SGC ^b	1200 mg q8h x 10 days	600 mg x 10 days	13	↓ (13%) [5-20%]	↓ (12%) [4-19%]
Azithromycin	600 mg single dose	400 mg x 7 days	14	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	12	↑ (11%) [3-19%]	↔
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↑ (16%) [6-26%]
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	11	↔	↔
Rifampin	600 mg x 7 days	600 mg x 7 days	12	↓ (20%) [11-28%]	↓ (26%) [15-36%]
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔
Cetirizine	10 mg single dose	600 mg x 10 days	11	↔	↓ (8%) [4-11%]
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↔
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔
Paroxetine	20 mg qd x 14 days	600 mg x 14 days	12	↔	↔
Sertraline	50 mg qd x 14 days	600 mg x 14 days	13	↑ (11%) [6-16%]	↔

146 ↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change

147 ^a Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for efavirenz alone.

148 ^b Soft Gelatin Capsule.

149

150 **INDICATIONS AND USAGE**

151 SUSTIVA (efavirenz) in combination with other antiretroviral agents is indicated for the
152 treatment of HIV-1 infection. This indication is based on two clinical trials of at least one
153 year duration that demonstrated prolonged suppression of HIV RNA.

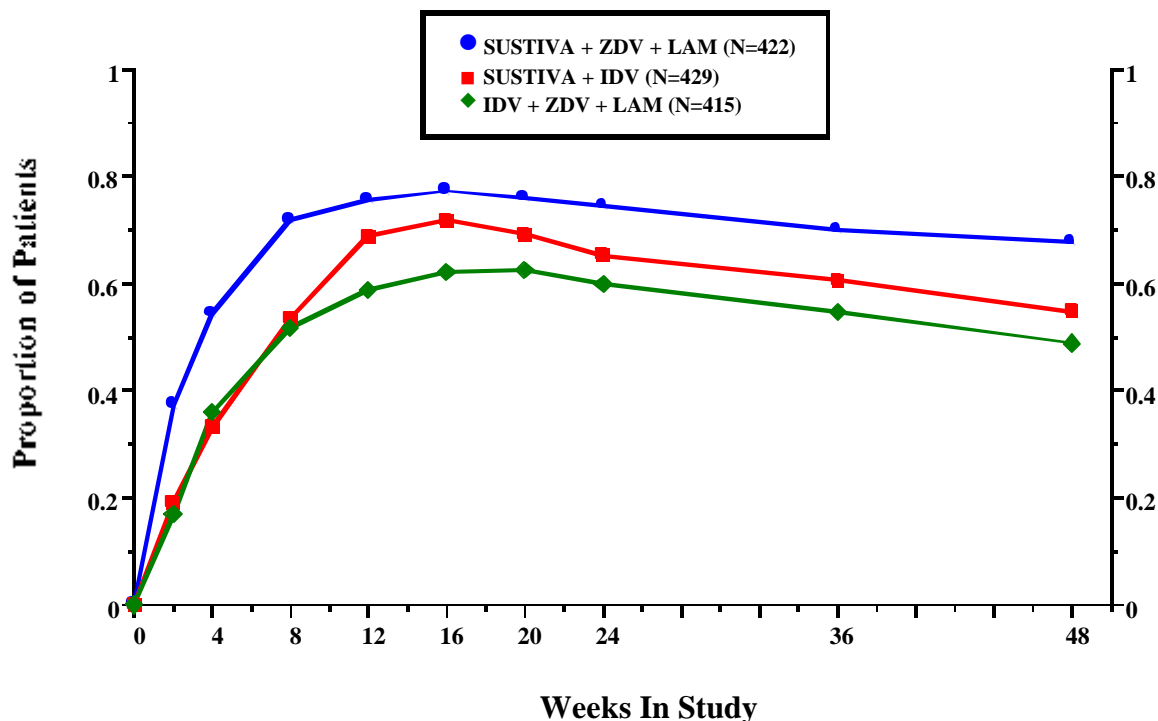
154 **Description of Studies**

155 In the two principal studies described below (Study 006 and ACTG 364), the response
156 was measured as the time to treatment failure (TTF). Plasma HIV-RNA levels were
157 quantified using the AMPLICOR HIV-1 MONITOR[®] (assay limit 400 copies/mL in
158 Study 006 and 500 copies/mL in ACTG 364).

159 **Study 006**, an ongoing, randomized, open-label trial, compares SUSTIVA (600
160 mg once daily) + indinavir (IDV, 1000 mg q8h) or SUSTIVA (600 mg once daily) +
161 zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) with indinavir (800
162 mg q8h) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h). Twelve hundred
163 sixty-six patients (mean age 36.5 years [range 18-81], 60% Caucasian, 83% male) were
164 enrolled. All patients were efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry.
165 The mean baseline CD4 cell count was 341 cells/mm³ and the mean baseline HIV-RNA
166 level was 60,250 copies/mL. There was no significant difference in mean CD4 cell count
167 among the treatment groups; the overall mean increase was approximately 200 cells at 48
168 weeks among patients who continued on study regimens. Treatment response and
169 outcomes through 48 weeks are shown in Figure 1 and Table 3, respectively.

170 **Figure 1**

Study 006: Treatment Response



- 171 • Proportion of patients at each time point who have HIV RNA <400 copies, who are on their original
172 study medication, and who have not experienced an AIDS-defining event.

173

Table 3: Study 006 - Outcomes of Randomized Treatment Through 48 Weeks

Outcome	SUSTIVA + ZDV + LAM n =422	SUSTIVA + IDV n=429	IDV + ZDV + LAM n=415
HIV-RNA <400 copies/mL (<50 ^a copies/mL)	68% (62%)	55% (49%)	49% (43%)
HIV-RNA ≥400 copies/mL ^b	6%	14%	11%
CDC Category C Event ^b	3%	2%	2%
Discontinuations for Adverse Events ^{b,c}	8%	8%	17%
Discontinuations for Other Reasons ^{b,d}	15%	22%	21%

174 ^a Ultrasensitive HIV-1 MONITOR assay.

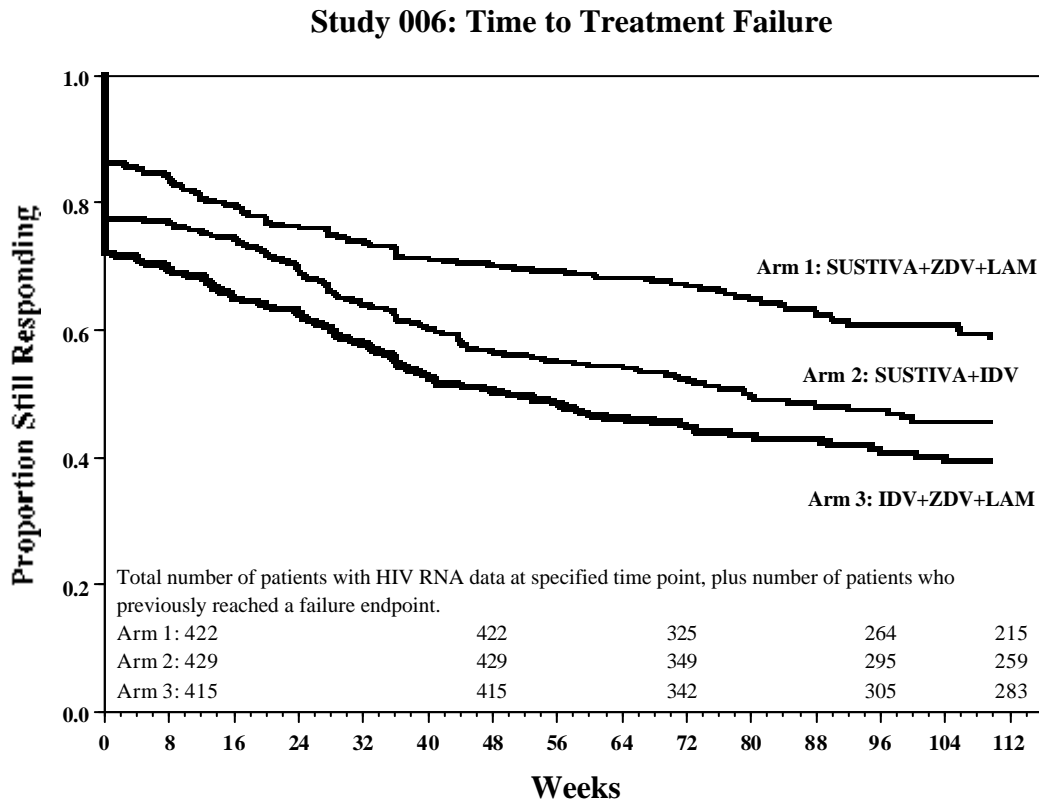
175 ^b These rates reflect events that were counted as the initial reason for treatment failure in the analysis.

176 ^c See **ADVERSE REACTIONS** for a description of the safety profile of these regimens.

177 ^d Consent withdrawn, lost to follow-up, missing data or protocol violation.

178 In addition to the complete 48-week follow-up data reported above, longer-term
 179 data are shown in Figure 2. This analysis allows for the inclusion of data beyond 48
 180 weeks as Kaplan-Meier estimates by accounting for patients who have not reached 112
 181 weeks of follow-up.

182 **Figure 2**



183
 184

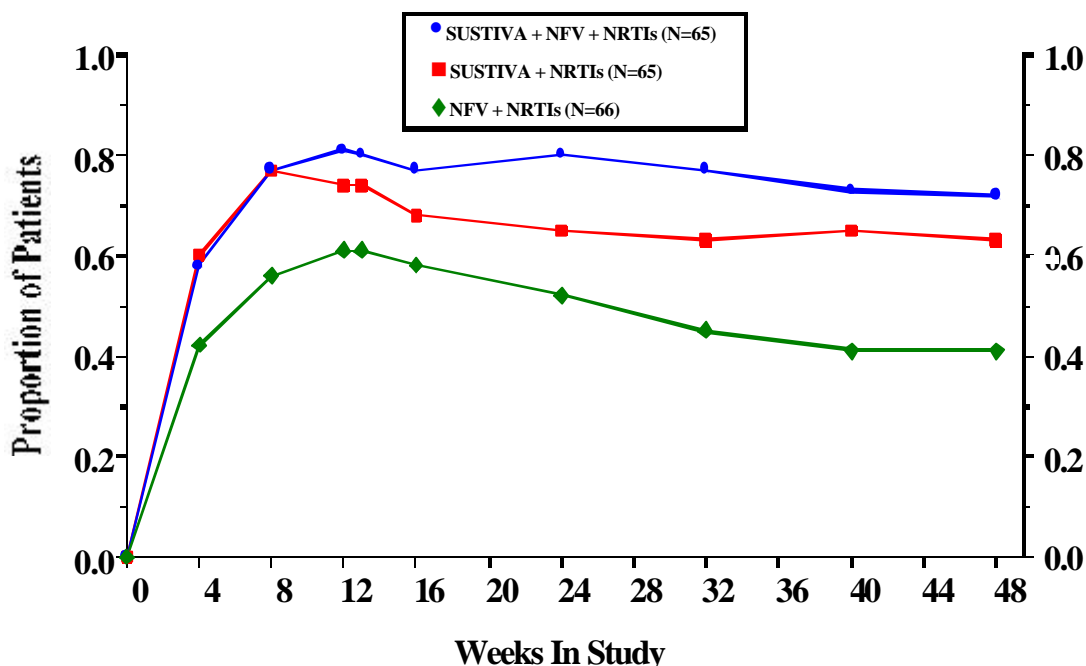
- 185 • Subjects were considered to have reached the study endpoint at the first time they either experienced
 186 virologic rebound (two HIV RNA values ≥ 400 copies), had an AIDS-defining clinical event, or
 187 discontinued study medication.
- 188 • Subjects who did not respond to initial treatment (no HIV RNA values < 400 copies) were considered
 189 to have reached this endpoint at time zero.

190 **ACTG 364** is a randomized, double-blind, placebo-controlled 48-week study in
 191 NRTI-experienced patients who had completed two prior ACTG studies. One-hundred
 192 ninety-six patients (mean age 41 years [range 18-76], 74% Caucasian, 88% male)
 193 received NRTIs in combination with SUSTIVA (efavirenz) (600 mg once daily), or
 194 nelfinavir (NFV, 750 mg TID), or SUSTIVA (600 mg once daily) + nelfinavir in a
 195 randomized, double-blinded manner. The mean baseline CD4 cell count was
 196 389 cells/mm³ and mean baseline HIV RNA level was 8130 copies/mL. Upon entry into

197 the study, all patients were assigned a new open-label NRTI regimen, which was
198 dependent on their previous NRTI treatment experience. There was no significant
199 difference in the mean CD4 cell count among treatment groups; the overall mean increase
200 was approximately 100 cells at 48 weeks among patients who continued on study
201 regimens. Treatment response and outcomes are shown in Figure 3 and Table 4,
202 respectively.

203 **Figure 3**

Study ACTG 364: Treatment Response



204

- 205 • Proportion of patients at each time point who have HIV RNA <500 copies confirmed by two
206 consecutive observations and are on their original study medication and who have not experienced an
207 AIDS-defining event.

208

Table 4: Study ACTG 364 - Outcomes of Randomized Treatment Through 48 Weeks*

Outcome	SUSTIVA + NFV + NRTIs n=65	SUSTIVA + NRTIs n=65	NFV + NRTIs n=66
HIV-RNA <500 copies/mL ^a	71%	63%	41%
HIV-RNA ≥500 copies/mL ^b	17%	34%	54%
CDC Category C Event	2%	0%	0%
Discontinuations for Adverse Events ^c	3%	3%	5%
Discontinuations for Other Reasons ^d	8%	0%	0%

209 * For some patients, Week 56 data were used to confirm the status at Week 48.

210 ^a Subjects achieved virologic response (two consecutive viral loads <500 copies/mL) and maintained it
 211 through Week 48.

212 ^b Includes viral rebound and failure to achieve confirmed <500 copies/mL by Week 48.

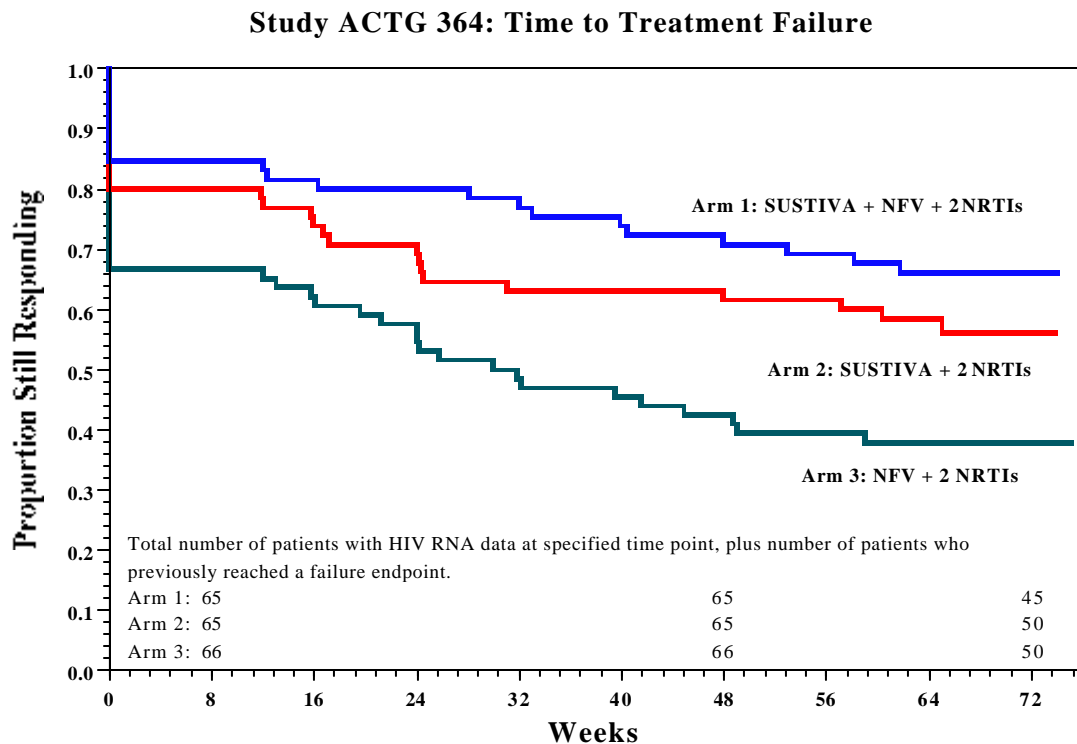
213 ^c See **ADVERSE REACTIONS** for a safety profile of these regimens.

214 ^d Includes loss to follow-up, consent withdrawn, noncompliance.

215 In addition to the complete 48-week data reported above, longer-term data are shown in
 216 Figure 4. This analysis allows for the inclusion of data beyond 48 weeks as Kaplan-Meier
 217 estimates by accounting for patients who have not reached 72 weeks of follow-up.

218

219 **Figure 4**



220

- 221 • Subjects were considered to have reached the study endpoint at the first time they either experienced
- 222 virologic rebound (two HIV RNA values ≥ 500 copies), had an AIDS-defining clinical event, or
- 223 discontinued study medication.
- 224 • Subjects who did not respond to initial treatment (no HIV RNA values ≤ 500 copies) were considered
- 225 to have reached this endpoint at time zero.
- 226 • The initial plateaus through Week 12 are due to the virologic testing schedule and the lack of dropouts
- 227 during this interval.

228 **CONTRAINDICATIONS**

229 SUSTIVA (efavirenz) is contraindicated in patients with clinically significant
 230 hypersensitivity to any of its components.

231 SUSTIVA should not be administered concurrently with astemizole, cisapride,
 232 midazolam, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz
 233 could result in inhibition of metabolism of these drugs and create the potential for serious
 234 and/or life-threatening adverse events (eg, cardiac arrhythmias, prolonged sedation, or
 235 respiratory depression).

236

237 **WARNINGS**

238 **ALERT: Find out about medicines that should NOT be taken with SUSTIVA.** This
239 statement is also included on the product's bottle labels. (See **CONTRAINDICATIONS**
240 and **PRECAUTIONS: Drug Interactions**.)

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

246 **Psychiatric Symptoms:** Serious psychiatric adverse experiences have been reported
247 in patients treated with SUSTIVA. In controlled trials of 1008 patients treated with
248 regimens containing SUSTIVA for an average of 1.6 years and 635 patients treated with
249 control regimens for an average of 1.3 years, the frequency of specific serious psychiatric
250 events among patients who received SUSTIVA or control regimens, respectively, were:
251 severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), nonfatal suicide attempts
252 (0.4%, 0%), aggressive behavior (0.4%, 0.3%), paranoid reactions (0.4%, 0.3%), and
253 manic reactions (0.1%, 0%). Patients with a history of psychiatric disorders appear to be
254 at greater risk of these serious psychiatric adverse experiences, with the frequency of
255 each of the above events ranging from 0.3% for manic reactions to 2.0% for both severe
256 depression and suicidal ideation. There have also been occasional post-marketing reports
257 of death by suicide, delusions, and psychosis-like behavior, although a causal relationship
258 to the use of SUSTIVA cannot be determined from these reports. Patients with serious
259 psychiatric adverse experiences should seek immediate medical evaluation to assess the
260 possibility that the symptoms may be related to the use of SUSTIVA, and if so, to
261 determine whether the risks of continued therapy outweigh the benefits (see **ADVERSE**
262 **REACTIONS**).

263 **Nervous System Symptoms:** Fifty-three percent of patients receiving SUSTIVA in
264 controlled trials reported central nervous system symptoms compared to 25% of patients
265 receiving control regimens. These symptoms included, but were not limited to, dizziness
266 (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%),
267 abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in
268 2.0% of patients, and 2.1% of patients discontinued therapy as a result. These symptoms
269 usually begin during the first or second day of therapy and generally resolve after the first
270 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system

271 symptoms of at least moderate severity ranged from 5 to 9% in patients treated with
272 regimens containing SUSTIVA and from 3 to 5% in patients treated with a control
273 regimen. Patients should be informed that these common symptoms were likely to
274 improve with continued therapy and were not predictive of subsequent onset of the less
275 frequent psychiatric symptoms (see **WARNINGS: Psychiatric Symptoms**). Dosing at
276 bedtime may improve the tolerability of these nervous system symptoms (see **ADVERSE**
277 **REACTIONS** and **DOSAGE AND ADMINISTRATION**).

278 Patients receiving SUSTIVA should be alerted to the potential for additive central
279 nervous system effects when SUSTIVA is used concomitantly with alcohol or
280 psychoactive drugs.

281 Patients who experience central nervous system symptoms such as dizziness,
282 impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such
283 as driving or operating machinery.

284 **Drug Interactions:** Concomitant use of SUSTIVA and St. John's wort (*Hypericum*
285 *perforatum*) or St. John's wort-containing products is not recommended.
286 Coadministration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including
287 SUSTIVA, with St. John's wort is expected to substantially decrease NNRTI
288 concentrations and may result in suboptimal levels of efavirenz and lead to loss of
289 virologic response and possible resistance to efavirenz or to the class of NNRTIs.

290 **Reproductive Risk Potential:** Malformations have been observed in fetuses from
291 efavirenz-treated monkeys that received doses which resulted in plasma drug
292 concentrations similar to those in humans given 600 mg/day (see **PRECAUTIONS:**
293 **Pregnancy**); therefore, pregnancy should be avoided in women receiving SUSTIVA.
294 Barrier contraception should always be used in combination with other methods of
295 contraception (eg, oral or other hormonal contraceptives). Women of childbearing
296 potential should undergo pregnancy testing prior to initiation of SUSTIVA.

297 **PRECAUTIONS**

298 **General**

299 **Skin Rash:** In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg
300 SUSTIVA experienced new-onset skin rash compared with 17% (111/635) of patients
301 treated in control groups. Rash associated with blistering, moist desquamation, or
302 ulceration occurred in 0.9% (9/1008) of patients treated with SUSTIVA. The incidence of

303 Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in patients treated
304 with SUSTIVA in all studies and expanded access was 0.1%. The median time to onset
305 of rash in adults was 11 days and the median duration, 16 days. The discontinuation rate
306 for rash in clinical trials was 1.7% (17/1008). SUSTIVA should be discontinued in
307 patients developing severe rash associated with blistering, desquamation, mucosal
308 involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve
309 the tolerability and hasten the resolution of rash.

310 Rash was reported in 26 of 57 pediatric patients (46%) treated with SUSTIVA
311 capsules. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and
312 two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in
313 pediatric patients was 8 days. Prophylaxis with appropriate antihistamines prior to
314 initiating therapy with SUSTIVA in pediatric patients should be considered (see
315 **ADVERSE REACTIONS**).

316 **Liver Enzymes:** In patients with known or suspected history of hepatitis B or C
317 infection and in patients treated with other medications associated with liver toxicity,
318 monitoring of liver enzymes is recommended. In patients with persistent elevations of
319 serum transaminases to greater than five times the upper limit of the normal range, the
320 benefit of continued therapy with SUSTIVA (efavirenz) needs to be weighed against the
321 unknown risks of significant liver toxicity (see **ADVERSE REACTIONS: Laboratory**
322 **Abnormalities**).

323 Because of the extensive cytochrome P450-mediated metabolism of efavirenz and
324 limited clinical experience in patients with hepatic impairment, caution should be
325 exercised in administering SUSTIVA to these patients.

326 **Convulsions:** Convulsions have been observed infrequently in patients receiving
327 efavirenz, generally in the presence of known medical history of seizures. Patients who
328 are receiving concomitant anticonvulsant medications primarily metabolized by the liver,
329 such as phenytoin, carbamazepine, and phenobarbital, may require periodic monitoring of
330 plasma levels. Caution must be taken in any patient with a history of seizures.

331 *Animal toxicology:* Nonsustained convulsions were observed in 6 of 20 monkeys
332 receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those
333 in humans given the recommended dose.

334 **Cholesterol:** Monitoring of cholesterol and triglycerides should be considered in
335 patients treated with SUSTIVA (see **ADVERSE REACTIONS**).

336 **Fat Redistribution:** Redistribution/accumulation of body fat including central obesity,
337 dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast
338 enlargement, and "cushingoid appearance" have been observed in patients receiving
339 antiretroviral therapy. The mechanism and long-term consequences of these events are
340 currently unknown. A causal relationship has not been established.

341 **Information for Patients**

342 A statement to patients and healthcare providers is included on the product's bottle labels:
343 **ALERT: Find out about medicines that should NOT be taken with SUSTIVA.** A
344 Patient Package Insert (PPI) for SUSTIVA is available for patient information.

345 Patients should be informed that SUSTIVA is not a cure for HIV infection and
346 that they may continue to develop opportunistic infections and other complications
347 associated with HIV disease. Patients should be told that there are currently no data
348 demonstrating that SUSTIVA therapy can reduce the risk of transmitting HIV to others
349 through sexual contact or blood contamination.

350 Patients should be advised to take SUSTIVA every day as prescribed. SUSTIVA
351 must always be used in combination with other antiretroviral drugs. Patients should be
352 advised to take SUSTIVA on an empty stomach, preferably at bedtime. Taking
353 SUSTIVA with food increases efavirenz concentrations and may increase the frequency
354 of adverse events. Dosing at bedtime may improve the tolerability of nervous system
355 symptoms (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).
356 Patients should remain under the care of a physician while taking SUSTIVA.

357 Patients should be informed that central nervous system symptoms including
358 dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are
359 commonly reported during the first weeks of therapy with SUSTIVA. Dosing at bedtime
360 may improve the tolerability of these symptoms, and these symptoms are likely to
361 improve with continued therapy. Patients should be alerted to the potential for additive
362 central nervous system effects when SUSTIVA is used concomitantly with alcohol or
363 psychoactive drugs. Patients should be instructed that if they experience these symptoms
364 they should avoid potentially hazardous tasks such as driving or operating machinery (see
365 **WARNINGS: Nervous System Symptoms**). In clinical trials, patients who develop
366 central nervous system symptoms were not more likely to subsequently develop
367 psychiatric symptoms (see **WARNINGS: Psychiatric Symptoms**).

368 Patients should also be informed that serious psychiatric symptoms including
369 severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and
370 psychosis-like symptoms have also been infrequently reported in patients receiving
371 SUSTIVA. Patients should be informed that if they experience severe psychiatric adverse
372 experiences they should seek immediate medical evaluation to assess the possibility that
373 the symptoms may be related to the use of SUSTIVA, and if so, to determine whether
374 discontinuation of SUSTIVA may be required. Patients should also inform their
375 physician of any history of mental illness or substance abuse (see **WARNINGS:**
376 **Psychiatric Symptoms**).

377 Patients should be informed that another common side effect is rash. These rashes
378 usually go away without any change in treatment. In a small number of patients, rash may
379 be serious. Patients should be advised that they should contact their physician promptly if
380 they develop a rash.

381 Because malformations have been observed in fetuses from efavirenz-treated
382 animals, instructions should be given to avoid pregnancy in women receiving SUSTIVA.
383 Women should be advised to notify their physician if they become pregnant while taking
384 SUSTIVA. A reliable form of barrier contraception should always be used in
385 combination with other methods of contraception, including oral or other hormonal
386 contraception, because the effects of efavirenz on hormonal contraceptives are not fully
387 characterized.

388 SUSTIVA may interact with some drugs; therefore, patients should be advised to
389 report to their doctor the use of any other prescription, nonprescription medication or
390 herbal products, particularly St. John's wort.

391 Patients should be informed that redistribution or accumulation of body fat may
392 occur in patients receiving antiretroviral therapy and that the cause and long-term health
393 effects of these conditions are not known at this time.

394 **Drug Interactions (see also CONTRAINDICATIONS and CLINICAL**
395 **PHARMACOLOGY: Drug Interactions)**

396 Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are
397 substrates of CYP3A4 may have decreased plasma concentrations when coadministered
398 with SUSTIVA. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19,
399 and 3A4 isozymes in the range of observed efavirenz plasma concentrations.
400 Coadministration of efavirenz with drugs primarily metabolized by these isozymes may

401 result in altered plasma concentrations of the coadministered drug. Therefore, appropriate
402 dose adjustments may be necessary for these drugs.

403 Drugs which induce CYP3A4 activity (eg, phenobarbital, rifampin, rifabutin)
404 would be expected to increase the clearance of efavirenz resulting in lowered plasma
405 concentrations. Drug interactions with SUSTIVA are summarized in Table 5.

Table 5^a

Drugs That Should Not Be Coadministered With SUSTIVA

Drug Class	Drugs Within Class Not To Be Coadministered With SUSTIVA
Antihistamines	astemizole
Benzodiazepines	midazolam, triazolam
GI Motility Agents	cisapride
Anti-Migraine	ergot derivatives

406

Established Drug Interactions

Drug Name	Effect	Clinical Comment
Clarithromycin	? clarithromycin concentration ? 14-OH metabolite concentration	Plasma concentrations decreased by SUSTIVA; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving SUSTIVA and clarithromycin. No dose adjustment of SUSTIVA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see Other Drugs , following table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with SUSTIVA.
Indinavir	? indinavir concentration	The optimal dose of indinavir, when given in combination with SUSTIVA, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to SUSTIVA. When indinavir at an increased dose (1000 mg every 8 hours) was given with SUSTIVA (600 mg once daily), the indinavir AUC and C _{min} were decreased on average by 33-46% and 39-57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Lopinavir/ritonavir	? lopinavir concentration	A dose increase of lopinavir/ritonavir to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food is recommended when used in combination with SUSTIVA.
Methadone	? methadone concentration	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Established Drug Interactions

Drug Name	Effect	Clinical Comment
Ethinyl estradiol	? ethinyl estradiol concentration	Plasma concentrations increased by SUSTIVA; clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.
Rifabutin	? rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	? efavirenz concentration	Clinical significance of reduced efavirenz concentrations unknown.
Ritonavir	? ritonavir concentration ? efavirenz concentration	Combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when SUSTIVA is used in combination with ritonavir.
Saquinavir	? saquinavir concentration	Should not be used as sole protease inhibitor in combination with SUSTIVA.
Sertraline	? sertraline concentration	Increases in sertraline dose should be guided by clinical response.

407

Other Potentially Clinically Significant Drug or Herbal Product Interactions With SUSTIVA^b

Anticoagulants: Warfarin	Plasma concentrations and effects potentially increased or decreased by SUSTIVA.
Anticonvulsants: Phenytoin Phenobarbital Carbamazepine	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antifungals: Itraconazole Ketoconazole	Drug interaction studies with SUSTIVA and these imidazole and triazole antifungals have not been conducted. SUSTIVA has the potential to decrease plasma concentrations of itraconazole and ketoconazole.
Anti-HIV protease inhibitors: Saquinavir/ritonavir combination Amprenavir	No pharmacokinetic data are available. SUSTIVA has the potential to decrease serum concentrations of amprenavir.
Non-nucleoside reverse transcriptase inhibitors	No studies have been performed with other NNRTIs.
St. John's wort (<i>hypericum perforatum</i>)	Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with SUSTIVA.

408

^a See Tables 1 and 2.

409

^b This table is not all-inclusive.

410

Other Drugs: Based on the results of drug interaction studies (see Tables 1 and 2), no

411

dosage adjustment is recommended when SUSTIVA is given with the following:

412 aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine,
413 fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, and zidovudine.

414 Specific drug interaction studies have not been performed with SUSTIVA and
415 NRTIs other than lamivudine and zidovudine. Clinically significant interactions would
416 not be expected since the NRTIs are metabolized via a different route than efavirenz and
417 would be unlikely to compete for the same metabolic enzymes and elimination pathways.

418 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

419 Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice
420 were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of
421 hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas
422 were increased above background in females. No increases in tumor incidence above
423 background were seen in males. In studies in which rats were administered efavirenz at
424 doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above
425 background were observed. The systemic exposure (based on AUCs) in mice was
426 approximately 1.7-fold that in humans receiving the 600-mg/day dose. The exposure in
427 rats was lower than that in humans. The mechanism of the carcinogenic potential is
428 unknown. However, in genetic toxicology assays, efavirenz showed no evidence of
429 mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These
430 included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation
431 assays in Chinese hamster ovary cells, chromosome aberration assays in human
432 peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone
433 marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the
434 relevance to humans of neoplasms in efavirenz-treated mice is not known.

435 Efavirenz did not impair mating or fertility of male or female rats, and did not
436 affect sperm of treated male rats. The reproductive performance of offspring born to
437 female rats given efavirenz was not affected. As a result of the rapid clearance of
438 efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or
439 below those achieved in humans given therapeutic doses of efavirenz.

440 **Pregnancy**

441 **Pregnancy Category C:** Pregnancy should be avoided in women receiving SUSTIVA.
442 Barrier contraception should always be used in combination with other methods of
443 contraception (eg, oral or other hormonal contraceptives). Women of childbearing

444 potential should undergo pregnancy testing prior to initiation of SUSTIVA (see
445 **WARNINGS: Reproductive Risk Potential**).

446 **Antiretroviral Pregnancy Registry:** To monitor fetal outcomes of pregnant
447 women exposed to SUSTIVA, an Antiretroviral Pregnancy Registry has been established.
448 Physicians are encouraged to register patients by calling (800) 258-4263.

449 There are no adequate and well-controlled studies in pregnant women. SUSTIVA
450 should be used during pregnancy only if the potential benefit justifies the potential risk to
451 the fetus, such as in pregnant women without other therapeutic options. As of July 2003,
452 the Antiretroviral Pregnancy Registry has received reports of 165 pregnancies exposed to
453 efavirenz-containing regimens, the majority of which were first-trimester exposures (160
454 pregnancies). Birth defects occurred in 4 of 142 live births (first-trimester exposure) and
455 0 of 11 live births (second/third-trimester exposure). In addition, there has been one
456 report of multiple defects including abnormalities consistent with Dandy-Walker
457 syndrome in a fetus from a spontaneous abortion, one report of neural tube defect in a
458 fetus from a pregnancy electively terminated in the second trimester, and one report of
459 meningomyelocele in an infant. All three mothers were exposed to efavirenz-containing
460 regimens in the first trimester. A causal relationship of these events to the use of
461 SUSTIVA cannot be established.

462 Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-
463 treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental
464 toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days
465 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug
466 concentrations similar to those in humans given 600 mg/day of SUSTIVA. Anencephaly
467 and unilateral anophthalmia were observed in one fetus, microphthalmia was observed
468 in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the
469 placenta in cynomolgus monkeys and produces fetal blood concentrations similar to
470 maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and
471 rabbits and produces fetal blood concentrations of efavirenz similar to maternal
472 concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses
473 that produced peak plasma concentrations and AUC values in female rats equivalent to or
474 lower than those achieved in humans given 600 mg once daily of SUSTIVA. Efavirenz
475 produced no reproductive toxicities when given to pregnant rabbits at doses that produced
476 peak plasma concentrations similar to and AUC values approximately half of those
477 achieved in humans given 600 mg once daily of SUSTIVA.

478 **Nursing Mothers**

479 **The Centers for Disease Control and Prevention recommend that HIV-infected**
480 **mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.**
481 Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into
482 the milk of lactating rats. Because of the potential for HIV transmission and the potential
483 for serious adverse effects in nursing infants, **mothers should be instructed not to**
484 **breast-feed if they are receiving SUSTIVA.**

485 **Pediatric Use**

486 ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to
487 characterize the safety, pharmacokinetics, and antiviral activity of SUSTIVA in
488 combination with nelfinavir (20-30 mg/kg TID) and NRTIs. Mean age was 8 years (range
489 3-16). SUSTIVA has not been studied in pediatric patients below 3 years of age or who
490 weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences was
491 generally similar to that of adult patients with the exception of a higher incidence of rash,
492 which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a
493 higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients
494 compared to 0.9% of adults (see **ADVERSE REACTIONS**, Table 7).

495 The starting dose of SUSTIVA was 600 mg once daily adjusted to body size,
496 based on weight, targeting AUC levels in the range of 190-380 $\mu\text{M}\cdot\text{h}$. The
497 pharmacokinetics of efavirenz in pediatric patients were similar to the pharmacokinetics
498 in adults who received 600-mg daily doses of SUSTIVA. In 48 pediatric patients
499 receiving the equivalent of a 600-mg dose of SUSTIVA, steady-state C_{max} was 14.2 ± 5.8
500 μM (mean \pm SD), steady-state C_{min} was 5.6 ± 4.1 μM , and AUC was 218 ± 104 $\mu\text{M}\cdot\text{h}$.

501 **Geriatric Use**

502 Clinical studies of SUSTIVA did not include sufficient numbers of subjects aged 65
503 years and over to determine whether they respond differently from younger subjects. In
504 general, dose selection for an elderly patient should be cautious, reflecting the greater
505 frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or
506 other therapy.

507 **ADVERSE REACTIONS**

508 The most significant adverse events observed in patients treated with SUSTIVA are
509 nervous system symptoms, psychiatric symptoms, and rash.

510 **Nervous System Symptoms:** Fifty-three percent of patients receiving SUSTIVA
511 reported central nervous system symptoms (see **WARNINGS: Nervous System**
512 **Symptoms**). Table 6 lists the frequency of the symptoms of different degrees of severity
513 and gives the discontinuation rates in clinical trials for one or more of the following
514 nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence,
515 abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor,
516 abnormal thinking, and depersonalization. The frequencies of specific central and
517 peripheral nervous system symptoms are provided in Table 8.

518

Table 6: Percent of Patients with One or More Selected Nervous System Symptoms^{a,b}

Percent of Patients with:	SUSTIVA 600 mg Once Daily	Control Groups
	(n=1008)	(n=635)
	%	%
Symptoms of any severity	52.7	24.6
Mild symptoms ^c	33.3	15.6
Moderate symptoms ^d	17.4	7.7
Severe symptoms ^e	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

519 ^a Includes events reported regardless of causality.

520 ^b Data from Study 006 and three Phase 2/3 studies.

521 ^c “Mild” = Symptoms which do not interfere with patient’s daily activities.

522 ^d “Moderate” = Symptoms which may interfere with daily activities.

523 ^e “Severe” = Events which interrupt patient’s usual daily activities.

524 **Psychiatric Symptoms:** Serious psychiatric adverse experiences have been reported in
525 patients treated with SUSTIVA. In controlled trials, the frequency of specific serious
526 psychiatric symptoms among patients who received SUSTIVA or control regimens,
527 respectively, were: severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), nonfatal
528 suicide attempts (0.4%, 0%), aggressive behavior (0.4%, 0.3%), paranoid reactions (0.4%,
529 0.3%), and manic reactions (0.1%, 0%) (see **WARNINGS: Psychiatric Symptoms**).
530 Additional psychiatric symptoms observed at a frequency of >2% among patients treated

531 with SUSTIVA or control regimens, respectively, in controlled clinical trials were depression
532 (15.8%, 13.1%), anxiety (11.1%, 7.6%), and nervousness (6.3%, 2.0%).

533 **Skin Rash:** Rashes are usually mild-to-moderate maculopapular skin eruptions that
534 occur within the first 2 weeks of initiating therapy with SUSTIVA. In most patients, rash
535 resolves with continuing SUSTIVA therapy within one month. SUSTIVA can be
536 reinitiated in patients interrupting therapy because of rash. Use of appropriate
537 antihistamines and/or corticosteroids may be considered when SUSTIVA is restarted.
538 SUSTIVA should be discontinued in patients developing severe rash associated with
539 blistering, desquamation, mucosal involvement, or fever. The frequency of rash by NCI
540 grade and the discontinuation rates as a result of rash are provided in Table 7.

Table 7: Percent of Patients with Treatment-Emergent Rash^{a,b}

Percent of Patients with:	Description of Rash Grade ^c	SUSTIVA 600 mg Once Daily Adults (n=1008)	SUSTIVA Pediatric Patients (n=57)	Control Groups Adults (n= 635)
		%	%	%
Rash of any grade	—	26.3	45.6	17.5
Grade 1 rash	Erythema, pruritus	10.7	8.8	9.8
Grade 2 rash	Diffuse maculopapular rash, dry desquamation	14.7	31.6	7.4
Grade 3 rash	Vesiculation, moist desquamation, ulceration	0.8	1.8	0.3
Grade 4 rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0.1	3.5	0.0
Treatment discontinuation as a result of rash	—	1.7	8.8	0.3

541 ^a Includes events reported regardless of causality.

542 ^b Data from Study 006 and three Phase 2/3 studies.

543 ^c NCI Grading System.

544 As seen in Table 7, rash is more common in pediatric patients and more often of
545 higher grade (ie, more severe) (see **PRECAUTIONS: General**).

546 Experience with SUSTIVA (efavirenz) in patients who discontinued other
547 antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued

548 nevirapine because of rash have been treated with SUSTIVA. Nine of these patients
549 developed mild-to-moderate rash while receiving therapy with SUSTIVA, and two of
550 these patients discontinued because of rash.

551 A few cases of pancreatitis have been described, although a causal relationship
552 with efavirenz has not been established. Asymptomatic increases in serum amylase levels
553 were observed in a significantly higher number of patients treated with efavirenz 600 mg
554 than in control patients (see **ADVERSE REACTIONS: Laboratory Abnormalities**).

555 Drug-related clinical adverse experiences of moderate or severe intensity
556 observed in $\geq 2\%$ of patients in two controlled clinical trials are presented in Table 8.

Table 8: Percent of Patients with Treatment-Emergent^a Adverse Events of Moderate or Severe Intensity Reported in $\geq 2\%$ of Patients in Studies 006 and ACTG 364

Adverse Events	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor-Naive Patients		
	SUSTIVA ^b + ZDV/LAM (n=412) %	SUSTIVA ^b + Indinavir (n=415) %	Indinavir + ZDV/LAM (n=401) %	SUSTIVA ^b + Nelfinavir + NRTIs (n=64) %	SUSTIVA ^b + NRTIs (n=65) %	Nelfinavir + NRTIs (n=66) %
Body as a Whole						
Fatigue	7	5	8	0	2	3
Pain	1	1	5	13	6	17
Central and Peripheral Nervous System						
Dizziness	8	8	3	2	6	6
Headache	7	4	4	5	2	3
Concentration impaired	5	2	0	0	0	0
Insomnia	6	7	3	0	0	2
Abnormal dreams	3	1	0	—	—	—
Somnolence	3	2	2	0	0	0
Anorexia	1	0	1	0	2	2
Gastrointestinal						
Nausea	12	7	25	3	2	2
Vomiting	7	6	14	—	—	—
Diarrhea	6	8	6	14	3	9
Dyspepsia	3	3	5	0	0	2
Abdominal pain	1	2	4	3	3	3

Table 8: Percent of Patients with Treatment-Emergent^a Adverse Events of Moderate or Severe Intensity Reported in ³2% of Patients in Studies 006 and ACTG 364

Adverse Events	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor -Naive Patients		
	SUSTIVA ^b + ZDV/LAM (n=412) %	SUSTIVA ^b + Indinavir (n=415) %	Indinavir + ZDV/LAM (n=401) %	SUSTIVA ^b + Nelfinavir + NRTIs (n=64) %	SUSTIVA ^b + NRTIs (n=65) %	Nelfinavir + NRTIs (n=66) %
Psychiatric						
Anxiety	1	3	0	—	—	—
Depression	2	1	0	3	0	5
Nervousness	2	2	0	2	0	2
Skin & Appendages						
Rash	13	20	7	9	5	9
Pruritus	0	1	1	9	5	9
Increased sweating	2	1	0	0	0	0

557 ^a Includes adverse events at least possibly related to study drug or of unknown relationship for Study 006.

558 Includes all adverse events regardless of relationship to study drug for Study ACTG 364.

559 ^b SUSTIVA provided as 600 mg once daily.

560 — = Not Specified.

561 ZDV = zidovudine, LAM=lamivudine.

562

563 In Study 006, lipodystrophy was reported in 2.3% of patients treated with
564 SUSTIVA + indinavir, 0.7% of patients treated with SUSTIVA + zidovudine +
565 lamivudine and 1.0% of patients treated with indinavir + zidovudine + lamivudine.

566 Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to
567 16 years who received SUSTIVA capsules, nelfinavir, and one or more NRTIs were: rash
568 (46%), diarrhea/loose stools (39%), fever (21%), cough (16%),
569 dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting
570 (12%), and headache (11%). The incidence of nervous system symptoms was 18%
571 (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five
572 patients (9%) discontinued because of rash (see also **PRECAUTIONS: Skin Rash** and
573 **Pediatric Use**).

574 Postmarketing Experience

575 *Body as a Whole:* allergic reactions, asthenia, redistribution/accumulation of body fat
576 (see **PRECAUTIONS: Fat Redistribution**)

577 *Central and Peripheral Nervous System:* abnormal coordination, ataxia, convulsions,
578 hypoesthesia, paresthesia, neuropathy, tremor

579 *Endocrine:* gynecomastia

580 *Gastrointestinal:* constipation, malabsorption

581 *Cardiovascular:* flushing, palpitations

582 *Liver and Biliary System:* hepatic enzyme increase, hepatic failure, hepatitis

583 *Metabolic and Nutritional:* hypercholesterolemia, hypertriglyceridemia

584 *Musculoskeletal:* arthralgia, myalgia, myopathy

585 *Psychiatric:* aggressive reactions, agitation, delusions, emotional lability, mania,
586 neurosis, paranoia, psychosis, suicide

587 *Respiratory:* dyspnea

588 *Skin and Appendages:* erythema multiforme, nail disorders, skin discoloration, Stevens-
589 Johnson syndrome

590 *Special Senses:* abnormal vision, tinnitus

591 **Laboratory Abnormalities**

592 *Liver Enzymes:* Among 1008 patients treated with 600 mg efavirenz in controlled clinical
593 trials, 3% developed AST levels and 3% developed ALT levels greater than five times
594 the upper limit of normal. Similar elevations of AST and ALT were seen in patients
595 treated with control regimens.

596 Liver function tests should be monitored in patients with a prior history of
597 hepatitis B and/or C. In 156 patients treated with 600 mg of SUSTIVA who were
598 seropositive for hepatitis B and/or C, 7% developed AST levels and 8% developed ALT
599 levels greater than five times the upper limit of normal. In 91 patients seropositive for
600 hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 4%
601 developed ALT elevations to these levels. Elevations of GGT to greater than five times
602 the upper limit of the normal range were observed in 4% of all patients treated with 600
603 mg of SUSTIVA and in 10% of patients seropositive for hepatitis B or C. In patients
604 treated with control regimens, the incidence of GGT elevations to this level was 1.5-2%,

605 irrespective of hepatitis B or C serology. Isolated elevations of GGT in patients receiving
606 SUSTIVA may reflect enzyme induction not associated with liver toxicity (see
607 **PRECAUTIONS: General**).

608 *Lipids:* Increases in total cholesterol of 10-20% have been observed in some uninfected
609 volunteers receiving SUSTIVA. In patients treated with SUSTIVA + zidovudine +
610 lamivudine, increases in nonfasting total cholesterol and HDL of approximately 20% and
611 25%, respectively, were observed. In patients treated with SUSTIVA + indinavir,
612 increases in nonfasting cholesterol and HDL of approximately 40% and 35%,
613 respectively, were observed. The effects of SUSTIVA on triglycerides and LDL were not
614 well characterized since samples were taken from nonfasting patients. The clinical
615 significance of these findings is unknown (see **PRECAUTIONS: General**).

616 *Serum Amylase:* Asymptomatic elevations in serum amylase greater than 1.5 times the
617 upper limit of normal were seen in 10% of patients treated with SUSTIVA and in 6% of
618 patients treated with control regimens. The clinical significance of asymptomatic
619 increases in serum amylase is unknown (see **ADVERSE REACTIONS**).

620 *Cannabinoid Test Interaction:* Efavirenz does not bind to cannabinoid receptors. False-
621 positive urine cannabinoid test results have been observed in non-HIV-infected
622 volunteers receiving SUSTIVA when the Microgenics CEDIA[®] DAU Multi-Level THC
623 assay was used for screening. Negative results were obtained when more specific
624 confirmatory testing was performed with gas chromatography/mass spectrometry.

625 Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THC assay,
626 Cannabinoid Enzyme Immunoassay [Diagnostic Reagents, Inc], and AxSYM[®]
627 Cannabinoid Assay), only the Microgenics CEDIA DAU Multi-Level THC assay showed
628 false-positive results. The other two assays provided true-negative results. The effects of
629 SUSTIVA on cannabinoid screening tests other than these three are unknown. The
630 manufacturers of cannabinoid assays should be contacted for additional information
631 regarding the use of their assays with patients receiving efavirenz.

CEDIA[®] is a registered trademark of Roche Diagnostics.

AxSYM[®] is a registered trademark of Abbott Laboratories.

632 **OVERDOSAGE**

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

635 Treatment of overdose with SUSTIVA (efavirenz) should consist of general
636 supportive measures, including monitoring of vital signs and observation of the patient's
637 clinical status. Administration of activated charcoal may be used to aid removal of
638 unabsorbed drug. There is no specific antidote for overdose with SUSTIVA. Since
639 efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug
640 from blood.

641 **DOSAGE AND ADMINISTRATION**

642 **Adults**

643 The recommended dosage of SUSTIVA is 600 mg orally, once daily, in combination
644 with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors
645 (NRTIs). It is recommended that SUSTIVA be taken on an empty stomach, preferably at
646 bedtime. The increased efavirenz concentrations observed following administration of
647 SUSTIVA with food may lead to an increase in frequency of adverse events (see
648 **CLINICAL PHARMACOLOGY: Effect of Food on Oral Absorption**). Dosing at
649 bedtime may improve the tolerability of nervous system symptoms (see **WARNINGS:**
650 **Nervous System Symptoms**, **PRECAUTIONS: Information for Patients**, and
651 **ADVERSE REACTIONS**).

652 **Concomitant Antiretroviral Therapy:** SUSTIVA must be given in combination with
653 other antiretroviral medications (see **CLINICAL PHARMACOLOGY: Drug**
654 **Interactions** and **PRECAUTIONS: Drug Interactions** and **INDICATIONS AND**
655 **USAGE**).

656 **Pediatric Patients**

657 It is recommended that SUSTIVA be taken on an empty stomach, preferably at bedtime.
658 Table 9 describes the recommended dose of SUSTIVA for pediatric patients 3 years of
659 age or older and weighing between 10 and 40 kg. The recommended dosage of
660 SUSTIVA for pediatric patients weighing greater than 40 kg is 600 mg, once daily.

Table 9: Pediatric Dose to be Administered Once Daily

Body Weight		SUSTIVA Dose (mg)
kg	lbs	
10 to <15	22 to <33	200
15 to <20	33 to <44	250
20 to <25	44 to <55	300
25 to <32.5	55 to <71.5	350
32.5 to <40	71.5 to <88	400
≥40	≥88	600

661 **HOW SUPPLIED**

662 **Capsules**

663 SUSTIVA[®] capsules are available as follows:

664 *Capsules 200 mg* are gold color, reverse printed with “SUSTIVA” on the body and
665 imprinted “200 mg” on the cap.

666 Bottles of 90 NDC 0056-0474-92

667 *Capsules 100 mg* are white, reverse printed with “SUSTIVA” on the body and imprinted
668 “100 mg” on the cap.

669 Bottles of 30 NDC 0056-0473-30

670 *Capsules 50 mg* are gold color and white, printed with “SUSTIVA” on the gold color cap
671 and reverse printed “50 mg” on the white body.

672 Bottles of 30 NDC 0056-0470-30

673 **Tablets**

674 SUSTIVA tablets are available as follows:

675 *Tablets 600 mg* are yellow, capsular-shaped, film-coated tablets, with "SUSTIVA"
676 printed on both sides.

677 Bottles of 30 NDC 0056-0510-30

678 SUSTIVA capsules and SUSTIVA tablets should be stored at 25° C (77° F); excursions
679 permitted to 15°–30° C (59°–86° F) [see USP Controlled Room Temperature].

680

681

682

683

684 Distributed by:
685 Bristol-Myers Squibb Company
686 Princeton, NJ 08543 USA

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692

Patient Information

693

SUSTIVA[®]* (sus-TEE-vah)

694

[efavirenz (eh-FAH-vih-rehnz)]

695

capsules and tablets

696

697

698 **ALERT: Find out about medicines that should NOT be taken with SUSTIVA.**

699 Please also read the section "**MEDICINES YOU SHOULD NOT TAKE WITH**
700 **SUSTIVA.**"

701 Read this information before you start taking SUSTIVA. Read it again each time you
702 refill your prescription, in case there is any new information. This leaflet provides a
703 summary about SUSTIVA and does not include everything there is to know about your
704 medicine. This information is not meant to take the place of talking with your doctor.

705 **What is SUSTIVA?**

706 SUSTIVA is a medicine used in combination with other medicines to help treat infection
707 with Human Immunodeficiency Virus (HIV), the virus that causes AIDS (acquired
708 immune deficiency syndrome). SUSTIVA is a type of anti-HIV drug called a "non-
709 nucleoside reverse transcriptase inhibitor" (NNRTI).

710 SUSTIVA works by lowering the amount of HIV in the blood (viral load).
711 SUSTIVA must be taken with other anti-HIV medicines. When taken with other anti-
712 HIV medicines, SUSTIVA has been shown to reduce viral load and increase the number
713 of CD4 cells, a type of immune cell in blood. SUSTIVA may not have these effects in
714 every patient.

715 SUSTIVA does not cure HIV or AIDS. People taking SUSTIVA may still
716 develop other infections and complications. Therefore, it is very important that you stay
717 under the care of your doctor.

718 SUSTIVA has not been shown to reduce the risk of passing HIV to others. Therefore,
719 continue to practice safe sex, and do not use or share dirty needles.

720 **What are the possible side effects of SUSTIVA?**

721 **Serious psychiatric problems.** A small number of patients experience severe depression,
722 strange thoughts, or angry behavior while taking SUSTIVA. Some patients have thoughts
723 of suicide and a few have actually committed suicide. These problems tend to occur more
724 often in patients who have had mental illness. Contact your doctor right away if you think
725 you are having these psychiatric symptoms, so your doctor can decide if you should
726 continue to take SUSTIVA.

727 **Common side effects.** Many patients have dizziness, trouble sleeping, drowsiness,
728 trouble concentrating, and/or unusual dreams during treatment with SUSTIVA. These
729 side effects may be reduced if you take SUSTIVA at bedtime on an empty stomach. They
730 also tend to go away after you have taken the medicine for a few weeks. If you have these
731 common side effects, such as dizziness, it does not mean that you will also have serious
732 psychiatric problems, such as severe depression, strange thoughts, or angry behavior. Tell
733 your doctor right away if any of these side effects continue or if they bother you. It is
734 possible that these symptoms may be more severe if SUSTIVA is used with alcohol or
735 mood altering (street) drugs.

736 If you are dizzy, have trouble concentrating, or are drowsy, avoid activities that
737 may be dangerous, such as driving or operating machinery.

738 Rash is common. Rashes usually go away without any change in treatment. In a
739 small number of patients, rash may be serious. If you develop a rash, call your doctor
740 right away. **Rash may be a serious problem in some children.** Tell your child's doctor
741 right away if you notice rash or any other side effects while your child is taking
742 SUSTIVA.

743 Other common side effects include tiredness, upset stomach, vomiting, and
744 diarrhea.

745 **Changes in body fat.** Changes in body fat develop in some patients taking anti-HIV
746 medicine. These changes may include an increased amount of fat in the upper back and
747 neck ("buffalo hump"), in the breasts, and around the trunk. Loss of fat from the legs,
748 arms, and face may also happen. The cause and long-term health effects of these fat
749 changes are not known.

750 Tell your doctor or healthcare provider if you notice any side effects while taking
751 SUSTIVA.

752 Contact your doctor before stopping SUSTIVA because of side effects or for any
753 other reason.

754 This is not a complete list of side effects possible with SUSTIVA. Ask your
755 doctor or pharmacist for a more complete list of side effects of SUSTIVA and all the
756 medicines you will take.

757 **How should I take SUSTIVA?**

758 **General Information**

- 759 • You should take SUSTIVA on an empty stomach, preferably at bedtime.
- 760 • Swallow SUSTIVA with water.
- 761 • Taking SUSTIVA with food increases the amount of medicine in your body, which
762 may increase the frequency of side effects.
- 763 • Taking SUSTIVA at bedtime may make some side effects less bothersome.
- 764 • SUSTIVA must be taken in combination with other anti-HIV medicines. If you take
765 only SUSTIVA, the medicine may stop working.
- 766 • Do not miss a dose of SUSTIVA. If you forget to take SUSTIVA, take the missed
767 dose right away, unless it is almost time for your next dose. Do not double the next
768 dose. Carry on with your regular dosing schedule. If you need help in planning the
769 best times to take your medicine, ask your doctor or pharmacist.
- 770 • Take the exact amount of SUSTIVA your doctor prescribes. Never change the dose
771 on your own. Do not stop this medicine unless your doctor tells you to stop.
- 772 • If you believe you took more than the prescribed amount of SUSTIVA, contact your
773 local Poison Control Center or emergency room right away.
- 774 • Tell your doctor if you start any new medicine or change how you take old ones.
775 Your doses may need adjustment.
- 776 • When your SUSTIVA supply starts to run low, get more from your doctor or
777 pharmacy. This is very important because the amount of virus in your blood may
778 increase if the medicine is stopped for even a short time. The virus may develop
779 resistance to SUSTIVA and become harder to treat.
- 780 • Your doctor may want to do blood tests to check for certain side effects while you
781 take SUSTIVA (efavirenz).

782 **Capsules**

- 783 • The dose of SUSTIVA capsules for adults is 600 mg (three 200-mg capsules, taken
784 together) once a day by mouth. The dose of SUSTIVA for children may be lower
785 (see **Can children take SUSTIVA?**).

786 **Tablets**

- 787 • The dose of SUSTIVA tablets for adults is 600 mg (one tablet) once a day by mouth.
788

789 **Can children take SUSTIVA?**

790 Yes, children who are able to swallow capsules can take SUSTIVA. Rash may be a
791 serious problem in some children. Tell your child's doctor right away if you notice rash
792 or any other side effects while your child is taking SUSTIVA. The dose of SUSTIVA for
793 children may be lower than the dose for adults. Capsules containing lower doses of
794 SUSTIVA are available. Your child's doctor will determine the right dose based on your
795 child's weight.

796 **Who should not take SUSTIVA?**

797 **Do not take SUSTIVA if you are allergic** to the active ingredient, efavirenz, or to any
798 of the inactive ingredients. Your doctor and pharmacist have a list of the inactive
799 ingredients.

800 **What should I avoid while taking SUSTIVA?**

- 801 • **Women taking SUSTIVA should not become pregnant.** Serious birth defects have
802 been seen in animals treated with SUSTIVA. It is not known whether this could
803 happen in humans. **Tell your doctor right away if you are pregnant.** Also talk with
804 your doctor if you want to become pregnant.
- 805 • Women should not rely only on hormone-based birth control, such as pills, injections,
806 or implants, because SUSTIVA may make these contraceptives ineffective. Women
807 must use a reliable form of barrier contraception, such as a condom or diaphragm,
808 even if they also use other methods of birth control.
- 809 • **Do not breast-feed if you are taking SUSTIVA.** The Centers for Disease Control
810 and Prevention recommend that mothers with HIV not breast-feed because they can
811 pass the HIV through their milk to the baby. Also, SUSTIVA may pass through
812 breast milk and cause serious harm to the baby. Talk with your doctor if you are
813 breast-feeding. You may need to stop breast-feeding or use a different medicine.
- 814 • Taking SUSTIVA with alcohol or other medicines causing similar side effects as
815 SUSTIVA, such as drowsiness, may increase those side effects.

- 816 • Do not take any other medicines without checking with your doctor. These medicines
817 include prescription and nonprescription medicines and herbal products, especially
818 St. John's wort.

819 **Before using SUSTIVA, tell your doctor if you**

- 820 • **have problems with your liver, or have hepatitis.** Your doctor may want to do tests
821 to check your liver while you take SUSTIVA.
- 822 • **have ever had mental illness or are using drugs or alcohol.**
- 823 • **have ever had seizures or are taking medicine for seizures** [for example, Dilantin[®]
824 (phenytoin), Tegretol[®] (carbamazepine), or phenobarbital]. Your doctor may want to
825 check drug levels in your blood from time to time.

826 **What important information should I know about taking other**
827 **medicines with SUSTIVA?**

828 **SUSTIVA may change the effect of other medicines, including ones for HIV, and**
829 **cause serious side effects.** Your doctor may change your other medicines or change
830 their doses. Other medicines, including herbal products, may affect SUSTIVA. For this
831 reason, **it is very important to:**

- 832 • let all your doctors and pharmacists know that you take SUSTIVA.
- 833 • tell your doctors and pharmacists about all medicines you take. This includes those
834 you buy over-the-counter and herbal or natural remedies.

835 Bring all your prescription and nonprescription medicines as well as any herbal
836 remedies that you are taking when you see a doctor, or make a list of their names, how
837 much you take, and how often you take them. This will give your doctor a complete
838 picture of the medicines you use. Then he or she can decide the best approach for your
839 situation.

840 Taking SUSTIVA with St. John's wort (*hypericum perforatum*), an herbal product
841 sold as a dietary supplement, or products containing St. John's wort is not recommended.
842 Talk with your doctor if you are taking or are planning to take St. John's wort. Taking St.
843 John's wort may decrease SUSTIVA levels and lead to increased viral load and possible
844 resistance to SUSTIVA or cross-resistance to other anti-HIV drugs.

845 **MEDICINES YOU SHOULD NOT TAKE WITH SUSTIVA**

846 The following medicines may cause serious and life-threatening side effects when taken
847 with SUSTIVA. You should not take any of these medicines while taking SUSTIVA:

- 848 • Hismanal[®] (astemizole)

- 849 • Propulsid[®] (cisapride)
- 850 • Versed[®] (midazolam)
- 851 • Halcion[®] (triazolam)
- 852 • Ergot medications (for example, Wigraine[®] and Cafergot[®])

853 The following medicines may need to be replaced with another medicine when taken
854 with SUSTIVA:

- 855 • Fortovase[®], Invirase[®] (saquinavir)
- 856 • Biaxin[®] (clarithromycin)

857 The following medicines may need to have their dose changed when taken with
858 SUSTIVA:

- 859 • Crixivan[®] (indinavir)
- 860 • Kaletra[®] (lopinavir/ritonavir)
- 861 • Methadone
- 862 • Mycobutin[®] (rifabutin)
- 863 • Zoloft[®] (sertraline)

864 **These are not all the medicines that may cause problems if you take SUSTIVA.**
865 **Be sure to tell your doctor about all medicines that you take.**

866 **General advice about SUSTIVA:**

867 **Medicines are sometimes prescribed for conditions that are not mentioned in patient**
868 **information leaflets. Do not use SUSTIVA for a condition for which it was not**
869 **prescribed. Do not give SUSTIVA to other people, even if they have the same**
870 **symptoms you have. It may harm them.**

871 Keep SUSTIVA at room temperature (77° F) in the bottle given to you by your
872 pharmacist. The temperature can range from 59° to 86° F.

873 Keep SUSTIVA out of the reach of children.

874

875 This leaflet summarizes the most important information about SUSTIVA. If you
876 would like more information, talk with your doctor. You can ask your pharmacist or
877 doctor for the full prescribing information about SUSTIVA, or you can visit the
878 SUSTIVA website at <http://www.sustiva.com> or call 1-800-426-7644.

879

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