

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

3 **Rx only**

4 **DESCRIPTION**

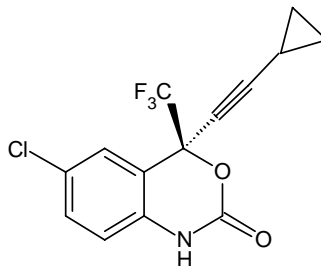
5 SUSTIVA[®] (efavirenz) is a human immunodeficiency virus type 1 (HIV-1) specific, non-
6 nucleoside, reverse transcriptase inhibitor (NNRTI).

7 **Capsules:** SUSTIVA is available as capsules for oral administration containing either
8 50 mg 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-dihydro-4-
21 (trifluoromethyl)-2H-3,1-benzoxazin-2-one.

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



23

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

26 **MICROBIOLOGY**

27 **Mechanism of Action**

28 Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human
29 immunodeficiency virus type 1 (HIV-1). EFV activity is mediated predominantly by
30 noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human
31 cellular DNA polymerases α , β , γ , and δ are not inhibited by EFV.

32 **Antiviral Activity in Cell Culture**

33 The concentration of EFV inhibiting replication of wild-type laboratory adapted strains
34 and clinical isolates in cell culture by 90-95% (EC_{90-95}) ranged from 1.7 to 25 nM in
35 lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and
36 macrophage/monocyte cultures. EFV demonstrated antiviral activity against most non-
37 clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity
38 against group O viruses. EFV demonstrated additive antiviral activity without
39 cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine
40 (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine
41 [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV]), PIs (amprenavir, indinavir
42 [IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide.
43 EFV demonstrated additive to antagonistic antiviral activity in cell culture with
44 atazanavir. EFV was not antagonistic with adefovir, used for the treatment of hepatitis B
45 virus infection, or ribavirin, used in combination with interferon for the treatment of
46 hepatitis C virus infection.

47 **Resistance**

48 **In cell culture:** In cell culture, HIV-1 isolates with reduced susceptibility to EFV
49 (>380-fold increase in EC₉₀ value) emerged rapidly in the presence of drug. Genotypic
50 characterization of these viruses identified mutations resulting in single amino acid
51 substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions
52 L100I/V179D/Y181C in RT.

53 **Clinical studies:** Clinical isolates with reduced susceptibility in cell culture to EFV
54 have been obtained. One or more RT substitutions at amino acid positions 98, 100, 101,
55 103, 106, 108, 188, 190, 225, and 227 were observed in patients failing treatment with
56 EFV in combination with IDV, or with ZDV plus LAM. The mutation K103N was the
57 most frequently observed. Long-term resistance surveillance (average 52 weeks, range
58 4-106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one
59 percent (17/28) of these failure isolates had decreased EFV susceptibility in cell culture
60 with a median 88-fold change in EFV susceptibility (EC₅₀ value) from reference. The
61 most frequent NNRTI mutation to develop in these patient isolates was K103N (54%).
62 Other NNRTI mutations that developed included L100I (7%), K101E/Q/R (14%), V108I
63 (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

64 **Cross-Resistance**

65 Cross-resistance among NNRTIs has been observed. Clinical isolates previously
66 characterized as EFV-resistant were also phenotypically resistant in cell culture to DLV
67 and NVP compared to baseline. DLV- and/or NVP-resistant clinical viral isolates with
68 NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A,
69 Y181X, Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to
70 EFV in cell culture. Greater than 90% of NRTI-resistant clinical isolates tested in cell
71 culture retained susceptibility to EFV.

72 **CLINICAL PHARMACOLOGY**73 **Pharmacokinetics**

74 **Absorption:** Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by
75 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected
76 volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg;
77 the increases were less than proportional suggesting diminished absorption at higher
78 doses.

79 In HIV-infected patients at steady state, mean C_{max} , mean C_{min} , and mean AUC were
80 dose proportional following 200-mg, 400-mg, and 600-mg daily doses. Time-to-peak
81 plasma concentrations were approximately 3-5 hours and steady-state plasma
82 concentrations were reached in 6-10 days. In 35 patients receiving SUSTIVA 600 mg
83 once daily, steady-state C_{max} was $12.9 \pm 3.7 \mu\text{M}$ (mean \pm SD), steady-state C_{min} was
84 $5.6 \pm 3.2 \mu\text{M}$, and AUC was $184 \pm 73 \mu\text{M}\cdot\text{h}$.

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

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

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

98 **Distribution:** Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma
99 proteins, predominantly albumin. In HIV-1 infected patients (n=9) who received

100 SUSTIVA 200 to 600 mg once daily for at least one month, cerebrospinal fluid
101 concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma
102 concentration. This proportion is approximately 3-fold higher than the non-protein-bound
103 (free) fraction of efavirenz in plasma.

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

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

114 **Elimination:** Efavirenz has a terminal half-life of 52-76 hours after single doses and 40-
115 55 hours after multiple doses. A one-month mass balance/excretion study was conducted
116 using 400 mg per day with a ¹⁴C-labeled dose administered on Day 8. Approximately 14-
117 34% of the radiolabel was recovered in the urine and 16-61% was recovered in the feces.
118 Nearly all of the urinary excretion of the radiolabeled drug was in the form of
119 metabolites. Efavirenz accounted for the majority of the total radioactivity measured in
120 feces.

121 **Special Populations**

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

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

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

130 **Geriatric:** see **PRECAUTIONS: Geriatric Use**

131 **Pediatrics:** see **PRECAUTIONS: Pediatric Use**

132 **Drug Interactions (see also CONTRAINDICATIONS and**
133 **PRECAUTIONS: Drug Interactions)**

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

145 Drug interaction studies were performed with efavirenz and other drugs likely to be
146 coadministered or drugs commonly used as probes for pharmacokinetic interaction. The
147 effects of coadministration of efavirenz on the C_{max} , AUC, and C_{min} are summarized in
148 Table 1 (effect of efavirenz on other drugs) and Table 2 (effect of other drugs on
149 efavirenz). For information regarding clinical recommendations see **PRECAUTIONS:**
150 **Drug Interactions.**

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ 59% (49-67%)	↓ 74% (68-78%)	↓ 93% (90-95%)
	400 mg qd d 1-6, then 300 mg qd d 7-20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7-20	13	↑ 14% ^a (↓ 17-↑ 58%)	↑ 39% ^a (2-88%)	↑ 48% ^a (24-76%)

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)			
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)	
Indinavir	1000 mg q8h x 10 days	600 mg x 10 days	20				
				After morning dose	↔ ^b	↓ 33% ^b (26-39%)	↓ 39% ^b (24-51%)
				After afternoon dose	↔ ^b	↓ 37% ^b (26-46%)	↓ 52% ^b (47-57%)
	After evening dose			↓ 29% ^b (11-43%)	↓ 46% ^b (37-54%)	↓ 57% ^b (50-63%)	
Lopinavir/ ritonavir	400/100 mg capsule q12h x 9 days	600 mg x 9 days	11,7 ^c	↔ ^d	↓ 19% ^d (↓ 36-↑ 3%)	↓ 39% ^d (3-62%)	
	600/150 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg x 9 days	23	↑ 36% ^d (28-44%)	↑ 36% ^d (28-44%)	↑ 32% ^d (21-44%)	
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%)	↓ 37% (25-48%)	↓ 43% (21-59%)	
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	11	After AM dose	↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%) ^e
				After PM dose	↔	↔	↑ 24% (3-50%) ^e
Saquinavir SGC ^f	1200 mg q8h x 10 days	600 mg x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%) ^e	
Lamivudine	150 mg q12h x 14 days	600 mg x 14 days	9	↔	↔	↑ 265% (37-873%)	
Tenofovir ^g	300 mg qd	600 mg x 14 days	29	↔	↔	↔	
Zidovudine	300 mg q12h x 14 days	600 mg x 14 days	9	↔	↔	↑ 225% (43-640%)	
Azithromycin	600 mg single dose	400 mg x 7 days	14	↑ 22% (4-42%)	↔	NA	
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)	
				14-OH metabolite	↑ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↔	↔	

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
Itraconazole	200 mg q12h x 28 days	600 mg x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxyitraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg x 9 days	NA	↓ 61% ^h	↓ 77% ^h	NA
	300 mg po q12h days 2-7	300 mg x 7 days	NA	↓ 36% ⁱ (21-49%)	↓ 55% ⁱ (45-62%)	NA
	400 mg po q12h days 2-7	300 mg x 7 days	NA	↑ 23% ⁱ (↓ 1-↑ 53%)	↓ 7% ⁱ (↓ 23-↑ 13%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg x 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)
Pravastatin	40 mg qd x 4 days	600 mg x 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg x 15 days	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA ^j
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg x 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Epoxide metabolite				↔	↔	↓ 13% (↓ 30-↑ 7%)
Cetirizine	10 mg single dose	600 mg x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg x 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodesmethyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↑ 37% (25-51%)	NA
Lorazepam	2 mg single dose	600 mg x 10 days	12	↑ 16% (2-32%)	↔	NA

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
Methadone	Stable maintenance 35-100 mg daily	600 mg x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
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%)	↓ 46% (31-58%)

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.

^a Compared with atazanavir 400 mg qd alone.

^b Comparator dose of indinavir was 800 mg q8h x 10 days.

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

^d Values are for lopinavir; the pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

^e 95% CI.

^f Soft Gelatin Capsule.

^g Tenofovir disoproxil fumarate.

^h 90% CI not available.

ⁱ Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).

^j Not available because of insufficient data.

NA = not available.

151

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (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%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↓ 12% (↓ 32-↑ 13%) ^b	↓ 12% (↓ 35-↑ 18%) ^b	↓ 21% (↓ 53-↑ 33%)
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%) ^b
Saquinavir SGC ^c	1200 mg q8h x 10 days	600 mg x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%) ^b
Tenofovir ^d	300 mg qd	600 mg x 14 days	30	↔	↔	↔
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%)	↔	↔

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h x 14 days	600 mg x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg x 7 days	600 mg x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg x 9 days	NA	↑ 38% ^e	↑ 44% ^e	NA
	300 mg po q12h days 2-7	300 mg x 7 days	NA	↓ 14% ^f (7-21%)	↔ ^f	NA
	400 mg po q12h days 2-7	300 mg x 7 days	NA	↔ ^f	↑ 17% ^f (6-29%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg x 15 days	14	↓ 12% (↓ 28-↑ 8%)	↔	↓ 12% (↓ 25-↑ 3%)
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg x 10 days	11	↔	↔	↔
Diltiazem	240 mg x 14 days	600 mg x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↔	↔
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
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%)	↔	↔

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90%CI)

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.

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

^b 95% CI.

^c Soft Gelatin Capsule.

^d Tenofovir disoproxil fumarate.

^e 90% CI not available.

^f Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

NA = not available.

152

153 **INDICATIONS AND USAGE**

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

157 **Description of Studies**

158 **Study 006**, a randomized, open-label trial, compared SUSTIVA (600 mg once daily) +
 159 zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) or SUSTIVA
 160 (600 mg once daily) + indinavir (IDV, 1000 mg q8h) with indinavir (800 mg q8h) +
 161 zidovudine (300 mg q12h) + lamivudine (150 mg q12h). Twelve hundred sixty-six
 162 patients (mean age 36.5 years [range 18-81], 60% Caucasian, 83% male) were enrolled.
 163 All patients were efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The
 164 median baseline CD4+ cell count was 320 cells/mm³ and the median baseline HIV-1
 165 RNA level was 4.8 log₁₀ copies/mL. Treatment outcomes with standard assay (assay
 166 limit 400 copies/mL) through 48 and 168 weeks are shown in Table 3. Plasma HIV RNA
 167 levels were quantified with standard (assay limit 400 copies/mL) and ultrasensitive (assay
 168 limit 50 copies/mL) versions of the AMPLICOR HIV-1 MONITOR[®] assay. During the
 169 study, version 1.5 of the assay was introduced in Europe to enhance detection of non-
 170 clade B virus.

Table 3: Outcomes of Randomized Treatment Through 48 and 168 Weeks, Study 006

Outcome	SUSTIVA + ZDV + LAM n=422		SUSTIVA + IDV n=429		IDV + ZDV + LAM n=415	
	Week 48	Week 168	Week 48	Week 168	Week 48	Week 168
Responder ^a	69%	48%	57%	40%	50%	29%
Virologic failure ^b	6%	12%	15%	20%	13%	19%
Discontinued for adverse events	7%	8%	6%	8%	16%	20%
Discontinued for other reasons ^c	17%	31%	22%	32%	21%	32%
CD4+ cell count (cells/mm ³)						
Observed subjects (n)	(279)	(205)	(256)	(158)	(228)	(129)
Mean change from baseline	190	329	191	319	180	329

171 ^a Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 or Week
172 168.

173 ^b Includes patients who rebounded, patients who were on study at Week 48 and failed to achieve
174 confirmed HIV-1 RNA <400 copies/mL at time of discontinuation, and patients who discontinued due to
175 lack of efficacy.

176 ^c Includes consent withdrawn, lost to follow-up, noncompliance, never treated, missing data, protocol
177 violation, death, and other reasons. Patients with HIV-1 RNA levels <400 copies/mL who chose not to
178 continue in the voluntary extension phases of the study were censored at date of last dose of study
179 medication.

180 For patients treated with SUSTIVA + zidovudine + lamivudine, SUSTIVA + indinavir,
181 or indinavir + zidovudine + lamivudine, the percentage of responders with HIV-1 RNA
182 <50 copies/mL was 65%, 50%, and 45%, respectively, through 48 weeks, and 43%, 31%,
183 and 23%, respectively, through 168 weeks. A Kaplan-Meier analysis of time to loss of
184 virologic response (HIV RNA <400 copies/mL) suggests that both the trends of virologic
185 response and differences in response continue through 4 years.

186 **ACTG 364** is a randomized, double-blind, placebo-controlled, 48-week study in NRTI-
187 experienced patients who had completed two prior ACTG studies. One-hundred ninety-
188 six patients (mean age 41 years [range 18-76], 74% Caucasian, 88% male) received
189 NRTIs in combination with SUSTIVA (efavirenz) (600 mg once daily), or nelfinavir
190 (NFV, 750 mg TID), or SUSTIVA (600 mg once daily) + nelfinavir in a randomized,
191 double-blinded manner. The mean baseline CD4+ cell count was 389 cells/mm³ and
192 mean baseline HIV-1 RNA level was 8130 copies/mL. Upon entry into the study, all
193 patients were assigned a new open-label NRTI regimen, which was dependent on their

194 previous NRTI treatment experience. There was no significant difference in the mean
 195 CD4+ cell count among treatment groups; the overall mean increase was approximately
 196 100 cells at 48 weeks among patients who continued on study regimens. Treatment
 197 outcomes are shown in Table 4. Plasma HIV RNA levels were quantified with the
 198 AMPLICOR HIV-1 MONITOR[®] assay using a lower limit of quantification of
 199 500 copies/mL.

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

Outcome	SUSTIVA + NFV + NRTIs n=65	SUSTIVA + NRTIs n=65	NFV + NRTIs n=66
HIV-1 RNA <500 copies/mL ^a	71%	63%	41%
HIV-1 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%

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

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

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

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

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

206 A Kaplan-Meier analysis of time to treatment failure through 72 weeks demonstrates a
 207 longer duration of virologic suppression (HIV RNA <500 copies/mL) in the SUSTIVA-
 208 containing treatment arms.

209 **CONTRAINDICATIONS**

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

212 SUSTIVA should not be administered concurrently with astemizole, bepridil, cisapride,
 213 midazolam, pimozide, triazolam, or ergot derivatives because competition for CYP3A4
 214 by efavirenz could result in inhibition of metabolism of these drugs and create the
 215 potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias,

216 prolonged sedation, or respiratory depression). SUSTIVA should not be administered
217 concurrently with standard doses of voriconazole because SUSTIVA significantly
218 decreases voriconazole plasma concentrations. Adjusted doses of voriconazole and
219 efavirenz may be administered concomitantly (see **CLINICAL PHARMACOLOGY**,
220 Tables 1 and 2; **PRECAUTIONS: Drug Interactions**, Table 5; and **DOSAGE AND**
221 **ADMINISTRATION: Dosage Adjustment**).

222 **WARNINGS**

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

226 SUSTIVA must not be used as a single agent to treat HIV-1 infection or added on as a
227 sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase
228 inhibitors, resistant virus emerges rapidly when efavirenz is administered as
229 monotherapy. The choice of new antiretroviral agents to be used in combination with
230 efavirenz should take into consideration the potential for viral cross-resistance.

231 Coadministration of SUSTIVA with ATRIPLA™ (efavirenz, emtricitabine, and tenofovir
232 disoproxil fumarate) is not recommended, since efavirenz is one of its active ingredients.

233 **Psychiatric Symptoms:** Serious psychiatric adverse experiences have been reported
234 in patients treated with SUSTIVA. In controlled trials of 1008 patients treated with
235 regimens containing SUSTIVA for a mean of 2.1 years and 635 patients treated with
236 control regimens for a mean of 1.5 years, the frequency of specific serious psychiatric
237 events among patients who received SUSTIVA or control regimens, respectively, were:
238 severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts
239 (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic
240 reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were
241 combined and evaluated as a group in a multifactorial analysis of data from Study 006,
242 treatment with efavirenz was associated with an increase in the occurrence of these
243 selected psychiatric symptoms. Other factors associated with an increase in the
244 occurrence of these psychiatric symptoms were history of injection drug use, psychiatric
245 history, and receipt of psychiatric medication at study entry; similar associations were
246 observed in both the SUSTIVA and control treatment groups. In Study 006, onset of new

247 serious psychiatric symptoms occurred throughout the study for both SUSTIVA-treated
248 and control-treated patients. One percent of SUSTIVA-treated patients discontinued or
249 interrupted treatment because of one or more of these selected psychiatric symptoms.
250 There have also been occasional postmarketing reports of death by suicide, delusions, and
251 psychosis-like behavior, although a causal relationship to the use of SUSTIVA cannot be
252 determined from these reports. Patients with serious psychiatric adverse experiences
253 should seek immediate medical evaluation to assess the possibility that the symptoms
254 may be related to the use of SUSTIVA, and if so, to determine whether the risks of
255 continued therapy outweigh the benefits (see **ADVERSE REACTIONS**).

256 **Nervous System Symptoms:** Fifty-three percent of patients receiving SUSTIVA in
257 controlled trials reported central nervous system symptoms compared to 25% of patients
258 receiving control regimens. These symptoms included, but were not limited to, dizziness
259 (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%),
260 abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in
261 2.0% of patients, and 2.1% of patients discontinued therapy as a result. These symptoms
262 usually begin during the first or second day of therapy and generally resolve after the first
263 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system
264 symptoms of at least moderate severity ranged from 5% to 9% in patients treated with
265 regimens containing SUSTIVA and from 3% to 5% in patients treated with a control
266 regimen. Patients should be informed that these common symptoms were likely to
267 improve with continued therapy and were not predictive of subsequent onset of the less
268 frequent psychiatric symptoms (see **WARNINGS: Psychiatric Symptoms**). Dosing at
269 bedtime may improve the tolerability of these nervous system symptoms (see **ADVERSE**
270 **REACTIONS** and **DOSAGE AND ADMINISTRATION**).

271 Analysis of long-term data from Study 006 (median follow-up 180 weeks, 102 weeks,
272 and 76 weeks for patients treated with SUSTIVA + zidovudine + lamivudine, SUSTIVA
273 + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond
274 24 weeks of therapy, the incidences of new-onset nervous system symptoms among
275 SUSTIVA-treated patients were generally similar to those in the indinavir-containing
276 control arm.

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

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

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

289 **Reproductive Risk Potential: Pregnancy Category D.** Efavirenz may cause fetal
290 harm when administered during the first trimester to a pregnant woman. Pregnancy
291 should be avoided in women receiving SUSTIVA. Barrier contraception should always
292 be used in combination with other methods of contraception (eg, oral or other hormonal
293 contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive
294 measures for 12 weeks after discontinuation of SUSTIVA is recommended. Women of
295 childbearing potential should undergo pregnancy testing before initiation of SUSTIVA. If
296 this drug is used during the first trimester of pregnancy, or if the patient becomes
297 pregnant while taking this drug, the patient should be apprised of the potential harm to
298 the fetus.

299 There are no adequate and well-controlled studies in pregnant women. SUSTIVA should
300 be used during pregnancy only if the potential benefit justifies the potential risk to the
301 fetus, such as in pregnant women without other therapeutic options. As of July 2007, the
302 Antiretroviral Pregnancy Registry has received prospective reports of 373 pregnancies
303 exposed to efavirenz-containing regimens, nearly all of which were first-trimester
304 exposures (359 pregnancies). Birth defects occurred in 7 of 295 live births (first-trimester
305 exposure) and 1 of 26 live births (second/third-trimester exposure). None of these
306 prospectively reported defects were neural tube defects. However, there have been five
307 retrospective reports of findings consistent with neural tube defects, including
308 meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the
309 first trimester. Although a causal relationship of these events to the use of SUSTIVA has
310 not been established, similar defects have been observed in preclinical studies of
311 efavirenz.

312 Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated
313 cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity
314 study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20-150)
315 with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations
316 similar to those in humans given 600 mg/day of SUSTIVA. Anencephaly and unilateral
317 anophthalmia were observed in one fetus, microphthalmia was observed in another
318 fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in
319 cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood
320 concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and
321 produces fetal blood concentrations of efavirenz similar to maternal concentrations. An
322 increase in fetal resorptions was observed in rats at efavirenz doses that produced peak
323 plasma concentrations and AUC values in female rats equivalent to or lower than those
324 achieved in humans given 600 mg once daily of SUSTIVA. Efavirenz produced no
325 reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma
326 concentrations similar to and AUC values approximately half of those achieved in
327 humans given 600 mg once daily of SUSTIVA.

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

331 **PRECAUTIONS**

332 **General**

333 **Skin Rash:** In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg
334 SUSTIVA experienced new-onset skin rash compared with 17% (111/635) of patients
335 treated in control groups. Rash associated with blistering, moist desquamation, or
336 ulceration occurred in 0.9% (9/1008) of patients treated with SUSTIVA. The incidence of
337 Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in patients treated
338 with SUSTIVA in all studies and expanded access was 0.1%. The median time to onset
339 of rash in adults was 11 days and the median duration, 16 days. The discontinuation rate
340 for rash in clinical trials was 1.7% (17/1008). SUSTIVA should be discontinued in
341 patients developing severe rash associated with blistering, desquamation, mucosal

342 involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the
343 tolerability and hasten the resolution of rash.

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

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

357 Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited
358 clinical experience in patients with hepatic impairment, caution should be exercised in
359 administering SUSTIVA (efavirenz) to these patients.

360 **Convulsions:** Convulsions have been observed in patients receiving efavirenz,
361 generally in the presence of known medical history of seizures. Caution must be taken in
362 any patient with a history of seizures. Patients who are receiving concomitant
363 anticonvulsant medications primarily metabolized by the liver, such as phenytoin and
364 phenobarbital, may require periodic monitoring of plasma levels (see **PRECAUTIONS:**
365 **Drug Interactions**).

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

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

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

376 **Immune Reconstitution Syndrome:** Immune reconstitution syndrome has been
377 reported in patients treated with combination antiretroviral therapy, including SUSTIVA.
378 During the initial phase of combination antiretroviral treatment, patients whose immune
379 system responds may develop an inflammatory response to indolent or residual
380 opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus,
381 *Pneumocystis jiroveci* pneumonia [PCP], or tuberculosis), which may necessitate further
382 evaluation and treatment.

383 **Information for Patients**

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

388 Patients should be informed that SUSTIVA is not a cure for HIV-1 infection and that
389 they may continue to develop opportunistic infections and other complications associated
390 with HIV-1 disease. Patients should be told that there are currently no data demonstrating
391 that SUSTIVA (efavirenz) therapy can reduce the risk of transmitting HIV to others
392 through sexual contact or blood contamination.

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

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

411 Patients should also be informed that serious psychiatric symptoms including severe
412 depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like
413 symptoms have also been reported in patients receiving SUSTIVA. Patients should be
414 informed that if they experience severe psychiatric adverse experiences they should seek
415 immediate medical evaluation to assess the possibility that the symptoms may be related
416 to the use of SUSTIVA, and if so, to determine whether discontinuation of SUSTIVA
417 may be required. Patients should also inform their physician of any history of mental
418 illness or substance abuse (see **WARNINGS: Psychiatric Symptoms**).

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

423 Women receiving SUSTIVA should be instructed to avoid pregnancy (see **WARNINGS:**
424 **Reproductive Risk Potential**). A reliable form of barrier contraception should always be
425 used in combination with other methods of contraception, including oral or other
426 hormonal contraception, because the effects of efavirenz on hormonal contraceptives are
427 not fully characterized. Because of the long half-life of efavirenz, use of adequate
428 contraceptive measures for 12 weeks after discontinuation of SUSTIVA is recommended.
429 Women should be advised to notify their physician if they become pregnant while taking
430 SUSTIVA. If this drug is used during the first trimester of pregnancy, or if the patient
431 becomes pregnant while taking this drug, she should be apprised of the potential harm to
432 the fetus.

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

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

439 **Drug Interactions (see also CONTRAINDICATIONS and**
440 **CLINICAL PHARMACOLOGY: Drug Interactions)**

441 Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are
442 substrates of CYP3A4 may have decreased plasma concentrations when coadministered
443 with SUSTIVA. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19,
444 and 3A4 isozymes in the range of observed efavirenz plasma concentrations.
445 Coadministration of efavirenz with drugs primarily metabolized by these isozymes may
446 result in altered plasma concentrations of the coadministered drug. Therefore, appropriate
447 dose adjustments may be necessary for these drugs.

448 Drugs which induce CYP3A4 activity (eg, phenobarbital, rifampin, rifabutin) would be
449 expected to increase the clearance of efavirenz resulting in lowered plasma
450 concentrations. Drug interactions with SUSTIVA are summarized in Tables 5 and 6. The
451 tables include potentially significant interactions, but are not all inclusive.

Table 5: Drugs That Are Contraindicated or Not Recommended for Use With SUSTIVA

Drug Class: Drug Name	Clinical Comment
Antifungal: voriconazole	CONTRAINDICATED at standard doses. SUSTIVA significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases SUSTIVA plasma concentrations, which may increase the risk of SUSTIVA-associated side effects. When voriconazole is coadministered with SUSTIVA, voriconazole maintenance dose should be increased to 400 mg every 12 hours and SUSTIVA dose should be decreased to 300 mg once daily using the capsule formulation. SUSTIVA tablets should not be broken. (See CLINICAL PHARMACOLOGY , Tables 1 and 2; CONTRAINDICATIONS ; and DOSAGE AND ADMINISTRATION: Dosage Adjustment .)
Antihistamine: astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort (<i>Hypericum perforatum</i>)	NOT RECOMMENDED: Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with SUSTIVA.

452

Table 6: Established^a and Other Potentially Significant^b Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of SUSTIVA or Concomitant Drug	Clinical Comment
<i>Antiretroviral agents</i>		
Protease inhibitor: Amprenavir	↓ amprenavir	SUSTIVA has the potential to decrease serum concentrations of amprenavir.
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when SUSTIVA is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when SUSTIVA is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir ^a	When coadministered with SUSTIVA in treatment-naive patients, the recommended dose of atazanavir is 300 mg with ritonavir 100 mg and SUSTIVA 600 mg (all once daily). Dosing recommendations for SUSTIVA and atazanavir in treatment-experienced patients have not been established.
Protease inhibitor: Indinavir	↓ indinavir ^a	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.

Table 6: Established^a and Other Potentially Significant^b Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of SUSTIVA or Concomitant Drug	Clinical Comment
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir ^a	Lopinavir/ritonavir tablets should not be administered once-daily in combination with SUSTIVA. In antiretroviral-naïve patients, lopinavir/ritonavir tablets can be used twice daily in combination with SUSTIVA with no dose adjustment. A dose increase of lopinavir/ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with SUSTIVA in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). A dose increase of lopinavir/ritonavir oral solution to 533/133 mg (6.5 mL) twice daily taken with food is recommended when used in combination with SUSTIVA.
Protease inhibitor: Ritonavir	↑ ritonavir ^a ↑ efavirenz ^a	When ritonavir 500 mg q12h was coadministered with SUSTIVA 600 mg once daily, the 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.
Protease inhibitor: Saquinavir	↓ saquinavir ^a	Should not be used as sole protease inhibitor in combination with SUSTIVA.
<i>Other agents</i>		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by SUSTIVA.
Anticonvulsants: Carbamazepine	↓ carbamazepine ^a ↓ efavirenz ^a	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ sertraline ^a	Increases in sertraline dose should be guided by clinical response.
Antifungals:		
Itraconazole	↓ itraconazole ^a ↓ hydroxyitraconazole ^a	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Table 6: Established^a and Other Potentially Significant^b Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of SUSTIVA or Concomitant Drug	Clinical Comment
Ketoconazole	↓ ketoconazole	Drug interaction studies with SUSTIVA and ketoconazole have not been conducted. SUSTIVA has the potential to decrease plasma concentrations of ketoconazole. (See Table 5 for guidance on coadministration with adjusted doses of voriconazole.)
Anti-infective: Clarithromycin	↓ clarithromycin ^a ↑ 14-OH metabolite ^a	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.
Antimycobacterial: Rifabutin	↓ rifabutin ^a	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimycobacterial: Rifampin	↓ efavirenz ^a	Clinical significance of reduced efavirenz concentrations is unknown. Dosing recommendations for concomitant use of SUSTIVA and rifampin have not been established.
Calcium channel blockers: Diltiazem	↓ diltiazem ^a ↓ desacetyl diltiazem ^a ↓ N-monodesmethyl diltiazem ^a	Diltiazem dose adjustments should be guided by clinical response (refer to the complete prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the complete prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin	↓ atorvastatin ^a ↓ pravastatin ^a	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.

Table 6: Established^a and Other Potentially Significant^b Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of SUSTIVA or Concomitant Drug	Clinical Comment
Simvastatin	↓ simvastatin ^a	
Narcotic analgesic: Methadone	↓ methadone ^a	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.
Oral contraceptive: Ethinyl estradiol	↑ ethinyl estradiol ^a	Plasma concentrations increased by SUSTIVA; clinical significance unknown. 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.

^a See **CLINICAL PHARMACOLOGY**, Tables 1 and 2 for magnitude of established interactions.

^b This table is not all-inclusive.

454

455 **Other Drugs:** Based on the results of drug interaction studies (see Tables 1 and 2), no
456 dosage adjustment is recommended when SUSTIVA (efavirenz) is given with the
457 following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine,
458 famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, tenofovir
459 disoproxil fumarate, and zidovudine.

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

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

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

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

486 **Pregnancy**487 **Pregnancy Category D: See WARNINGS: Reproductive Risk Potential.**488 **Nursing Mothers**489 **The Centers for Disease Control and Prevention recommend that HIV-infected**
490 **mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.**491 Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into
492 the milk of lactating rats. Because of the potential for HIV transmission and the potential
493 for serious adverse effects in nursing infants, **mothers should be instructed not to**
494 **breast-feed if they are receiving SUSTIVA.**495 **Pediatric Use**496 ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to
497 characterize the safety, pharmacokinetics, and antiviral activity of SUSTIVA (efavirenz)
498 in combination with nelfinavir (20-30 mg/kg TID) and NRTIs. Mean age was 8 years
499 (range 3-16). SUSTIVA has not been studied in pediatric patients below 3 years of age or
500 who weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences
501 was generally similar to that of adult patients with the exception of a higher incidence of
502 rash, which was reported in 46% (26/57) of pediatric patients compared to 26% of adults,
503 and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients
504 compared to 0.9% of adults (see **ADVERSE REACTIONS**, Table 8).505 The starting dose of SUSTIVA was 600 mg once daily adjusted to body size, based on
506 weight, targeting AUC levels in the range of 190-380 $\mu\text{M}\cdot\text{h}$. The pharmacokinetics of
507 efavirenz in pediatric patients were similar to the pharmacokinetics in adults who
508 received 600-mg daily doses of SUSTIVA. In 48 pediatric patients receiving the
509 equivalent of a 600-mg dose of SUSTIVA, steady-state C_{max} was $14.2 \pm 5.8 \mu\text{M}$
510 (mean \pm SD), steady-state C_{min} was $5.6 \pm 4.1 \mu\text{M}$, and AUC was $218 \pm 104 \mu\text{M}\cdot\text{h}$.

511 **Geriatric Use**

512 Clinical studies of SUSTIVA did not include sufficient numbers of subjects aged
513 65 years and over to determine whether they respond differently from younger subjects.
514 In general, dose selection for an elderly patient should be cautious, reflecting the greater
515 frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or
516 other therapy.

517 **ADVERSE REACTIONS**

518 The most significant adverse events observed in patients treated with SUSTIVA are
519 nervous system symptoms, psychiatric symptoms, and rash. Unless otherwise specified,
520 the analyses described below included 1008 patients treated with regimens containing
521 SUSTIVA and 635 patients treated with a control regimen in controlled trials.

522 **Nervous System Symptoms:** Fifty-three percent of patients receiving SUSTIVA
523 reported central nervous system symptoms (see **WARNINGS: Nervous System**
524 **Symptoms**). Table 7 lists the frequency of the symptoms of different degrees of severity
525 and gives the discontinuation rates in clinical trials for one or more of the following
526 nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence,
527 abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor,
528 abnormal thinking, and depersonalization. The frequencies of specific central and
529 peripheral nervous system symptoms are provided in Table 9.

Table 7: Percent of Patients with One or More Selected Nervous System Symptoms^{a,b}

Percent of Patients with:	SUSTIVA 600 mg Once Daily (n=1008) %	Control Groups (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

530 ^a Includes events reported regardless of causality.

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

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

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

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

535 **Psychiatric Symptoms:** Serious psychiatric adverse experiences have been reported in
 536 patients treated with SUSTIVA. In controlled trials, the frequency of specific serious
 537 psychiatric symptoms among patients who received SUSTIVA or control regimens,
 538 respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal
 539 suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%,
 540 0.3%), and manic reactions (0.2%, 0.3%) (see **WARNINGS: Psychiatric Symptoms**).
 541 Additional psychiatric symptoms observed at a frequency of >2% among patients treated
 542 with SUSTIVA or control regimens, respectively, in controlled clinical trials were depression
 543 (19%, 16%), anxiety (13%, 9%), and nervousness (7%, 2%).

544 **Skin Rash:** Rashes are usually mild-to-moderate maculopapular skin eruptions that
 545 occur within the first 2 weeks of initiating therapy with SUSTIVA. In most patients, rash
 546 resolves with continuing SUSTIVA therapy within one month. SUSTIVA can be
 547 reinitiated in patients interrupting therapy because of rash. Use of appropriate
 548 antihistamines and/or corticosteroids may be considered when SUSTIVA is restarted.
 549 SUSTIVA should be discontinued in patients developing severe rash associated with
 550 blistering, desquamation, mucosal involvement, or fever. The frequency of rash by NCI
 551 grade and the discontinuation rates as a result of rash are provided in Table 8.

Table 8: Percent of Patients with Treatment-Emergent Rash^{a,b}

Percent of Patients with:	Description of Rash Grade ^c	SUSTIVA 600 mg	SUSTIVA	Control
		Once Daily Adults (n=1008)	Pediatric Patients (n=57)	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

552 ^a Includes events reported regardless of causality.

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

554 ^c NCI Grading System.

555 As seen in Table 8, rash is more common in pediatric patients and more often of higher
556 grade (ie, more severe) (see **PRECAUTIONS: General**).

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

562 Pancreatitis has been reported, although a causal relationship with efavirenz has not been
563 established. Asymptomatic increases in serum amylase levels were observed in a
564 significantly higher number of patients treated with efavirenz 600 mg than in control
565 patients (see **ADVERSE REACTIONS: Laboratory Abnormalities**).

566 Selected clinical adverse experiences of moderate or severe intensity observed in $\geq 2\%$ of
567 SUSTIVA-treated patients in two controlled clinical trials are presented in Table 9.

Table 9: Selected Treatment-Emergent^a Adverse Events of Moderate or Severe Intensity Reported in ≥2% of SUSTIVA-Treated 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) 180 weeks ^c	SUSTIVA ^b + Indinavir (n=415) 102 weeks ^c	Indinavir + ZDV/LAM (n=401) 76 weeks ^c	SUSTIVA ^b + Nelfinavir + NRTIs (n=64) 71.1 weeks ^c	SUSTIVA ^b + NRTIs (n=65) 70.9 weeks ^c	Nelfinavir + NRTIs (n=66) 62.7 weeks ^c
Body as a Whole						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
Central and Peripheral Nervous System						
Dizziness	9%	9%	2%	2%	6%	6%
Headache	8%	5%	3%	5%	2%	3%
Insomnia	7%	7%	2%	0	0	2%
Concentration impaired	5%	3%	<1%	0	0	0
Abnormal dreams	3%	1%	0	—	—	—
Somnolence	2%	2%	<1%	0	0	0
Anorexia	1%	<1%	<1%	0	2%	2%
Gastrointestinal						
Nausea	10%	6%	24%	3%	2%	2%
Vomiting	6%	3%	14%	—	—	—
Diarrhea	3%	5%	6%	14%	3%	9%
Dyspepsia	4%	4%	6%	0	0	2%
Abdominal pain	2%	2%	5%	3%	3%	3%
Psychiatric						
Anxiety	2%	4%	<1%	—	—	—
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
Skin & Appendages						
Rash	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

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

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

570 ^b SUSTIVA provided as 600 mg once daily.

571 ^c Median duration of treatment.

572 — = Not Specified.

573 ZDV = zidovudine, LAM=lamivudine.

574 Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years

575 who received SUSTIVA (efavirenz) capsules, nelfinavir, and one or more NRTIs were:

576 rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%),
577 dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting
578 (12%), and headache (11%). The incidence of nervous system symptoms was 18%
579 (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five
580 patients (9%) discontinued because of rash (see also **PRECAUTIONS: Skin Rash** and
581 **Pediatric Use**).

582 **Postmarketing Experience**

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

585 *Central and Peripheral Nervous System:* abnormal coordination, ataxia, cerebellar
586 coordination and balance disturbances, convulsions, hypoesthesia, paresthesia,
587 neuropathy, tremor

588 *Endocrine:* gynecomastia

589 *Gastrointestinal:* constipation, malabsorption

590 *Cardiovascular:* flushing, palpitations

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

592 *Metabolic and Nutritional:* hypercholesterolemia, hypertriglyceridemia

593 *Musculoskeletal:* arthralgia, myalgia, myopathy

594 *Psychiatric:* aggressive reactions, agitation, delusions, emotional lability, mania,
595 neurosis, paranoia, psychosis, suicide

596 *Respiratory:* dyspnea

597 *Skin and Appendages:* erythema multiforme, nail disorders, photoallergic dermatitis, skin
598 discoloration, Stevens-Johnson syndrome

599 *Special Senses:* abnormal vision, tinnitus

600 **Laboratory Abnormalities**

601 Selected Grade 3-4 laboratory abnormalities reported in $\geq 2\%$ of SUSTIVA-treated
 602 patients in two clinical trials are presented in Table 10.

Table 10: Selected Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of SUSTIVA-Treated Patients in Studies 006 and ACTG 364

Variable	Limit	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients		
		SUSTIVA ^a + ZDV/LAM (n=412) 180 weeks ^b	SUSTIVA ^a + Indinavir (n=415) 102 weeks ^b	Indinavir + ZDV/LAM (n=401) 76 weeks ^b	SUSTIVA ^a + Nelfinavir + NRTIs (n=64) 71.1 weeks ^b	SUSTIVA ^a + NRTIs (n=65) 70.9 weeks ^b	Nelfinavir + NRTIs (n=66) 62.7 weeks ^b
Chemistry							
ALT	>5 x ULN	5%	8%	5%	2%	6%	3%
AST	>5 x ULN	5%	6%	5%	6%	8%	8%
GGT ^c	>5 x ULN	8%	7%	3%	5%	0	5%
Amylase	>2 x ULN	4%	4%	1%	0	6%	2%
Glucose	>250 mg/dL	3%	3%	3%	5%	2%	3%
Triglycerides ^d	≥ 751 mg/dL	9%	6%	6%	11%	8%	17%
Hematology							
Neutrophils	<750/mm ³	10%	3%	5%	2%	3%	2%

^a SUSTIVA provided as 600 mg once daily.

^b Median duration of treatment.

^c Isolated elevations of GGT in patients receiving SUSTIVA may reflect enzyme induction not associated with liver toxicity.

^d Nonfasting.

ZDV = zidovudine, LAM = lamivudine, ULN = Upper limit of normal, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyltransferase.

603 Liver function tests should be monitored in patients with a history of hepatitis B and/or C.
 604 In the long-term data set from Study 006, 137 patients treated with SUSTIVA-containing
 605 regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen
 606 (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface
 607 antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected

608 patients, elevations in AST to greater than five times ULN developed in 13% of patients
609 in the SUSTIVA arms and 7% of those in the control arm, and elevations in ALT to
610 greater than five times ULN developed in 20% of patients in the SUSTIVA arms and 7%
611 of patients in the control arm. Among co-infected patients, 3% of those treated with
612 SUSTIVA-containing regimens and 2% in the control arm discontinued from the study
613 because of liver or biliary system disorders (see **PRECAUTIONS: General**).

614 *Lipids:* Increases from baseline in total cholesterol of 10-20% have been observed in
615 some uninfected volunteers receiving SUSTIVA (efavirenz). In patients treated with
616 SUSTIVA + zidovudine + lamivudine, increases from baseline in nonfasting total
617 cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In
618 patients treated with SUSTIVA + indinavir, increases from baseline in nonfasting
619 cholesterol and HDL of approximately 40% and 35%, respectively, were observed.
620 Nonfasting total cholesterol levels ≥ 240 mg/dL and ≥ 300 mg/dL were reported in 34%
621 and 9%, respectively, of patients treated with SUSTIVA + zidovudine + lamivudine; 54%
622 and 20%, respectively, of patients treated with SUSTIVA + indinavir; and 28% and 4%,
623 respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of
624 SUSTIVA on triglycerides and LDL were not well characterized since samples were
625 taken from nonfasting patients. The clinical significance of these findings is unknown
626 (see **PRECAUTIONS: General**).

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

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

639 **OVERDOSAGE**

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

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

647 **DOSAGE AND ADMINISTRATION**

648 **Adults**

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

658 **Concomitant Antiretroviral Therapy:** SUSTIVA must be given in combination with
659 other antiretroviral medications (see **CLINICAL PHARMACOLOGY: Drug**
660 **Interactions** and **PRECAUTIONS: Drug Interactions** and **INDICATIONS AND**
661 **USAGE**).

662 **Dosage Adjustment:** If SUSTIVA is coadministered with voriconazole, the
663 voriconazole maintenance dose should be increased to 400 mg every 12 hours and the
664 SUSTIVA dose should be decreased to 300 mg once daily using the capsule formulation
665 (one 200-mg and two 50-mg capsules or six 50-mg capsules). SUSTIVA tablets should
666 not be broken. (See **CLINICAL PHARMACOLOGY**, Tables 1 and 2;
667 **CONTRAINDICATIONS**; and **PRECAUTIONS: Drug Interactions**.)

668 **Pediatric Patients**

669 It is recommended that SUSTIVA be taken on an empty stomach, preferably at bedtime.
 670 Table 11 describes the recommended dose of SUSTIVA for pediatric patients 3 years of
 671 age or older and weighing between 10 and 40 kg. The recommended dosage of
 672 SUSTIVA for pediatric patients weighing greater than 40 kg is 600 mg, once daily.

Table 11: 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

673 **HOW SUPPLIED**674 **Capsules**

675 SUSTIVA[®] (efavirenz) capsules are available as follows:

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

678 Bottles of 90 NDC 0056-0474-92

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

681 Bottles of 30 NDC 0056-0470-30

682 **Tablets**

683 SUSTIVA (efavirenz) tablets are available as follows:

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

686 Bottles of 30 NDC 0056-0510-30

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

689 Distributed by:

690 Bristol-Myers Squibb Company

691 Princeton, NJ 08543 USA

692 SUSTIVA is a registered trademark of Bristol-Myers Squibb Pharma Company.

693 ATRIPLA is a trademark of Bristol-Myers Squibb & Gilead Sciences, LLC.

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701 **PATIENT INFORMATION**

Rx only

702 **SUSTIVA**[®] (sus-TEE-vah)

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

704 **capsules and tablets**

705

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

707 Please also read the section "**MEDICINES YOU SHOULD NOT TAKE WITH**
708 **SUSTIVA.**"

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

713 **What is SUSTIVA?**

714 SUSTIVA is a medicine used in combination with other medicines to help treat infection
715 with Human Immunodeficiency Virus type 1 (HIV-1), the virus that causes AIDS
716 (acquired immune deficiency syndrome). SUSTIVA is a type of anti-HIV drug called a
717 "non-nucleoside reverse transcriptase inhibitor" (NNRTI). NNRTIs are not used in the
718 treatment of Human Immunodeficiency Virus type 2 (HIV-2) infection.

719 SUSTIVA works by lowering the amount of HIV-1 in the blood (viral load). SUSTIVA
720 must be taken with other anti-HIV medicines. When taken with other anti-HIV
721 medicines, SUSTIVA has been shown to reduce viral load and increase the number of
722 CD4+ cells, a type of immune cell in blood. SUSTIVA may not have these effects in
723 every patient.

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

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

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

730 **Serious psychiatric problems.** A small number of patients experience severe depression,
731 strange thoughts, or angry behavior while taking SUSTIVA. Some patients have thoughts
732 of suicide and a few have actually committed suicide. These problems tend to occur more
733 often in patients who have had mental illness. Contact your doctor right away if you think
734 you are having these psychiatric symptoms, so your doctor can decide if you should
735 continue to take SUSTIVA (efavirenz).

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

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

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

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

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

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

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

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

764 **How should I take SUSTIVA?**

765 **General Information**

- 766 • You should take SUSTIVA on an empty stomach, preferably at bedtime.
- 767 • Swallow SUSTIVA with water.
- 768 • Taking SUSTIVA with food increases the amount of medicine in your body, which
769 may increase the frequency of side effects.
- 770 • Taking SUSTIVA at bedtime may make some side effects less bothersome.
- 771 • SUSTIVA must be taken in combination with other anti-HIV medicines. If you take
772 only SUSTIVA, the medicine may stop working.
- 773 • Do not miss a dose of SUSTIVA. If you forget to take SUSTIVA, take the missed
774 dose right away, unless it is almost time for your next dose. Do not double the next
775 dose. Carry on with your regular dosing schedule. If you need help in planning the
776 best times to take your medicine, ask your doctor or pharmacist.
- 777 • Take the exact amount of SUSTIVA your doctor prescribes. Never change the dose
778 on your own. Do not stop this medicine unless your doctor tells you to stop.
- 779 • If you believe you took more than the prescribed amount of SUSTIVA, contact your
780 local Poison Control Center or emergency room right away.

- 781 • Tell your doctor if you start any new medicine or change how you take old ones.
782 Your doses may need adjustment.
- 783 • When your SUSTIVA supply starts to run low, get more from your doctor or
784 pharmacy. This is very important because the amount of virus in your blood may
785 increase if the medicine is stopped for even a short time. The virus may develop
786 resistance to SUSTIVA and become harder to treat.
- 787 • Your doctor may want to do blood tests to check for certain side effects while you
788 take SUSTIVA (efavirenz).

789 **Capsules**

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

793 **Tablets**

- 794 • The dose of SUSTIVA tablets for adults is 600 mg (one tablet) once a day by mouth.
795

796 **Can children take SUSTIVA?**

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

803 **Who should not take SUSTIVA?**

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

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

- 808 • **Women should not become pregnant while taking SUSTIVA and for 12 weeks**
809 **after stopping it.** Serious birth defects have been seen in the offspring of animals and
810 women treated with SUSTIVA during pregnancy. It is not known whether SUSTIVA
811 caused these defects. **Tell your doctor right away if you are pregnant.** Also talk
812 with your doctor if you want to become pregnant.
- 813 • Women should not rely only on hormone-based birth control, such as pills, injections,
814 or implants, because SUSTIVA may make these contraceptives ineffective. Women
815 must use a reliable form of barrier contraception, such as a condom or diaphragm,
816 even if they also use other methods of birth control. SUSTIVA may remain in your
817 blood for a time after therapy is stopped. Therefore, you should continue to use
818 contraceptive measures for 12 weeks after you stop taking SUSTIVA.
- 819 • **Do not breast-feed if you are taking SUSTIVA.** The Centers for Disease Control
820 and Prevention recommend that mothers with HIV not breast-feed because they can
821 pass the HIV through their milk to the baby. Also, SUSTIVA may pass through breast
822 milk and cause serious harm to the baby. Talk with your doctor if you are breast-
823 feeding. You may need to stop breast-feeding or use a different medicine.
- 824 • Taking SUSTIVA with alcohol or other medicines causing similar side effects as
825 SUSTIVA, such as drowsiness, may increase those side effects.
- 826 • Do not take any other medicines without checking with your doctor. These medicines
827 include prescription and nonprescription medicines and herbal products, especially
828 St. John's wort.

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

- 830 • **have problems with your liver or have hepatitis.** Your doctor may want to do tests
831 to check your liver while you take SUSTIVA.
- 832 • **have ever had mental illness or are using drugs or alcohol.**
- 833 • **have ever had seizures or are taking medicine for seizures** [for example, Dilantin[®]
834 (phenytoin), Tegretol[®] (carbamazepine), or phenobarbital]. Your doctor may want to
835 switch you to another medicine or check drug levels in your blood from time to time.

836 **What important information should I know about taking other**
837 **medicines with SUSTIVA?**

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

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

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

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

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

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

- 857 • Hismanal[®] (astemizole)
858 • Vascor[®] (bepridil)
859 • Propulsid[®] (cisapride)
860 • Versed[®] (midazolam)
861 • Orap[®] (pimozide)
862 • Halcion[®] (triazolam)
863 • Ergot medications (for example, Wigraine[®] and Cafergot[®])

864 The following medicine should not be taken with SUSTIVA since it may lose its effect or
865 may increase the chance of having side effects from SUSTIVA:

- 866 • Vfend[®] (voriconazole). Some doses of voriconazole can be taken at the same time as
867 a lower dose of SUSTIVA, but you must check with your doctor first.

868

869 The following medicine should not be taken with SUSTIVA since it contains efavirenz,
870 the active ingredient in SUSTIVA:

- 871 • ATRIPLA[™] (efavirenz, emtricitabine, tenofovir disoproxil fumarate)

872

873 **The following medicines may need to be replaced with another medicine when taken**
874 **with SUSTIVA:**

- 875 • Fortovase[®], Invirase[®] (saquinavir)
876 • Biaxin[®] (clarithromycin)
877 • Carbatrol[®], Tegretol[®] (carbamazepine)
878 • Sporanox[®] (itraconazole)

879 **The following medicines may require a change in the dose of either SUSTIVA or the**
880 **other medicine:**

- 881 • Calcium channel blockers such as Cardizem[®] or Tiazac[®] (diltiazem), Covera HS[®] or
882 Isoptin SR[®] (verapamil), and others.
883 • The cholesterol-lowering medicines Lipitor[®] (atorvastatin), PRAVACHOL[®]
884 (pravastatin sodium), and Zocor[®] (simvastatin).
885 • Crixivan[®] (indinavir)
886 • Kaletra[®] (lopinavir/ritonavir)
887 • Methadone
888 • Mycobutin[®] (rifabutin)
889 • REYATAZ[®] (atazanavir sulfate). If you are taking SUSTIVA and REYATAZ, you
890 should also be taking Norvir[®] (ritonavir).
891 • Rifadin[®] (rifampin) or the rifampin-containing medicines Rifamate[®] and Rifater[®].

892 • Zoloft[®] (sertraline)

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

895 **General advice about SUSTIVA:**

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

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

902 Keep SUSTIVA out of the reach of children.

903

904 This leaflet summarizes the most important information about SUSTIVA. If you would
905 like more information, talk with your doctor. You can ask your pharmacist or doctor for
906 the full prescribing information about SUSTIVA, or you can visit the SUSTIVA website
907 at <http://www.sustiva.com> or call 1-800-321-1335.

908 _____

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