

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%)
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%)
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%)

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

^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).

NA = not available.

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)
Itraconazole	200 mg q12h x 14 days	600 mg x 28 days	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)
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%)
Diltiazem	240 mg x 14 days	600 mg x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)

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

^e 90% CI not available.

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

NA = not available.

CONTRAINDICATIONS

SUSTIVA should not be administered concurrently with astemizole, bepridil, cisapride, midazolam, pimozide, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). SUSTIVA should not be administered concurrently with standard doses of voriconazole because SUSTIVA significantly decreases voriconazole plasma concentrations. Adjusted doses of voriconazole and efavirenz may be administered concomitantly (see **CLINICAL PHARMACOLOGY**, Tables 1 and 2; **PRECAUTIONS: Drug Interactions**, Table 5; and **DOSAGE AND ADMINISTRATION: Dosage Adjustment**).

PRECAUTIONS: Drug Interactions

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 .)
Calcium channel blocker: bepridil	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.

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
Antifungals:		
Itraconazole	↓ itraconazole ^a ↓ hydroxyitraconazole ^a	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole	Drug interaction studies with SUSTIVA and ketoconazole have not been conducted. SUSTIVA has the potential to decrease ketoconazole concentrations.
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).

DOSAGE AND ADMINISTRATION

Adults

Dosage Adjustment: If SUSTIVA is coadministered with voriconazole, the voriconazole maintenance dose should be increased to 400 mg every 12 hours and the SUSTIVA dose should be decreased to 300 mg once daily using the capsule formulation (three 100-mg capsules or one 200-mg and one 100-mg capsule). SUSTIVA tablets should not be broken. (See **CLINICAL PHARMACOLOGY**, Tables 1 and 2; **CONTRAINDICATIONS**; and **PRECAUTIONS: Drug Interactions**).