DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20972/S-042
NDA 21360/S-030

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Hwei-Gene Wang, Ph.D.
Associate Director, Global Regulatory and Safety Sciences, US
5 Research Parkway, Room 285B, Mailstop 2DW-206
Wallingford, CT 06492

Dear Dr. Wang:

Please refer to your Supplemental New Drug Applications (sNDAs) dated July 13, 2012, received July 13, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sustiva® (efavirenz) Capsules, 50 and 200 mg (NDA 20972) and Tablets, 600 mg (NDA 21360).

We also refer to our letter dated June 14, 2012, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to revised drug-drug interaction information based on additional review of drug-drug interaction data and the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes requested in our June 14, 2012 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Sustiva® (efavirenz) Capsules, 50 and 200 mg (NDA 20972) and Tablets, 600 mg (NDA 21360), consistent with our June 14, 2012 letter as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. The Product name in the **HIGHLIGHTS** section has been revised as follows:
   SUSTIVA® (efavirenz) capsules ~~capsules and tablets~~ for oral use
   SUSTIVA® (efavirenz) tablets for oral use

2. The **RECENT MAJOR CHANGES** in the **HIGHLIGHTS** section of the label has been revised as follows:

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Adults (2.1)	12/2011
Warnings and Precautions –	
Coadministration with Related Products (5.3)	00/0000
Rash (5.7)	06/2012
Immune Reconstitution Syndrome (5.11)	00/0000

3. The second bulleted paragraph in the **HIGHLIGHTS** section of the label has been revised as follows:

   - Not recommended with ATRIPLA, which contains efavirenz, emtricitabine, and tenofovir disoproxil fumarate, unless needed for dose adjustment when coadministered with rifampin. (5.3)

4. The revision date has been changed from 06/2012 to 00/0000 at the end of the **HIGHLIGHTS** section and the last page of the label.

5. The **WARNINGS AND PRECAUTIONS/Coadministration with Related Products** sub-section has been revised as follows:

   Coadministration of SUSTIVA with ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg) is not recommended unless needed for dose adjustment (eg, with rifampin), since efavirenz is one of its active ingredients.

6. The **WARNINGS AND PRECAUTIONS /Immune Reconstitution Syndrome** sub-section has been revised as follows:

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

   Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

7. The Table 7 in the **DRUG INTERACTIONS/Drug-Drug Interactions** sub-section has been revised as follows:

Table 7: 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	Clinical Comment
HIV a~~A~~nti~~retro~~viral agents		
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 sulfate	↓ atazanavir~~*a~~	*Treatment-naive patients:* When coadministered with SUSTIVA, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and SUSTIVA 600 mg (once daily on an empty stomach, preferably at bedtime). *Treatment-experienced patients:* Coadministration of SUSTIVA and atazanavir is not recommended.
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 7: 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	Clinical Comment
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir[*a]	Lopinavir/ritonavir tablets should not be administered once daily in combination with SUSTIVA. In antiretroviral-naive 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.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. SUSTIVA should not be coadministered with other NNRTIs.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc[*a]	Refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz.
Integrase strand transfer inhibitor: Raltegravir	↓ raltegravir[*]	SUSTIVA reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.

Table 7: 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	Clinical Comment
Hepatitis C antiviral agents		
Protease inhibitor: Boceprevir	↓ boceprevir*	Plasma trough concentrations of boceprevir were decreased when boceprevir was coadministered with SUSTIVA, which may result in loss of therapeutic effect. ~~Avoid combination.~~ The combination should be avoided.
Protease inhibitor: Telaprevir	↓ telaprevir* ↓ efavirenz*	Concomitant administration of telaprevir and SUSTIVA resulted in reduced steady-state exposures to telaprevir and efavirenz.
Other agents		
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.
Antidepressants: Bupropion	↓ bupropion~~[a]~~*	The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded.
Sertraline	↓ sertraline~~[a]~~*	Increases in sertraline dosage should be guided by clinical response.

Table 7: 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	Clinical Comment
Antifungals:		
Voriconazole	↓ voriconazole[a,*] ↑ efavirenz[a,*]	SUSTIVA and voriconazole must not be coadministered at standard doses. Efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz 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 *Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3, Tables 8* and *9)*.]
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 plasma concentrations of ketoconazole.
Posaconazole	↓ posaconazole[a,*]	Avoid concomitant use unless the benefit outweighs the risks.

Table 7: 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	Clinical Comment
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.
Antimycobacterials: 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.
Rifampin	↓ efavirenz[a,*]	If SUSTIVA is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of SUSTIVA to 800 mg once daily is recommended.
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 full 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 CYP3A. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin	↓ atorvastatin[a,*]	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Pravastatin	↓ pravastatin[a,*]	
Simvastatin	↓ simvastatin[a,*]	

Table 7: 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	Clinical Comment
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate	↓ active metabolites of norgestimate[a,*]	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
Implant Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓ immunosuppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction. These immunosuppressants are not anticipated to affect exposure of efavirenz. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.
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.

Table 7: 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	Clinical Comment

* The interaction between SUSTIVA and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

[a] ~~See *Clinical Pharmacology (12.3, Tables 8* and 9) for magnitude of established interactions.~~

[b] This table is not all-inclusive.

8. The Tables 8 and 9 in the **CLINICAL PHARMACOLOGY/Pharmacokinetics/Drug Interaction Studies** sub-section have been revised as follows:

Table 8: 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)
Maraviroc	100 mg bid	600 mg qd	12	↓ 51% (37-62%)	↓ 45% (38-51%)	↓ 45% (28-57%)
Raltegravir	400 mg single dose	600 mg qd	9	↓ 36% (2-59%)	↓ 36% (20-48%)	↓ 21% (↓ 51-↑ 28%)
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↓ 8% (↓ 22-↑ 8%)	↓ 19% (11-25%)	↓ 44% (26-58%)
Telaprevir	750 mg q8h x 10 days	600 mg qd x 20 days	21	↓ 9% (↓ 18-↑ 2%)	↓ 26% (16-35%)	↓ 47% (35-56%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↑ 22% (4-42%)	↔	NA

Table 9: 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)
Tenofovir[d]	300 mg qd	600 mg qd x 14 days	30	↔	↔	↔
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↑ 11% (2-20%)	↑ 20% (15-26%)	NA
Telaprevir	750 mg	600 mg qd	21	↓ 16%	↓ 7%	↓ 2%

Table 9: 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)	Efavirenz (mean % change) AUC (90% CI)	Efavirenz (mean % change) C_{min} (90% CI)
	q8h x 10 days	x 20 days		(7-24%)	(2-13%)	(↓ 6-↑ 2%)
Telaprevir, coadministered with tenofovir disoproxil fumarate (TDF)	1125 mg q8h x 7 days	600 mg efavirenz /300 mg TDF qd x 7 days	15	↓ 24% (15-32%)	↓ 18% (10-26%)	↓ 10% (↓ 19-↑ 1%)
	1500 mg q12h x 7 days	600 mg efavirenz /300 mg TDF qd x 7 days	16	↓ 20% (14-26%)	↓ 15% (9-21%)	↓ 11% (4-18%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔

9. The **PATIENT COUNSELING INFORMATION/General Information for Patients** sub-section has been revised as follows:

Patients should be informed that SUSTIVA is not a cure for HIV-1 infection and ~~that they~~patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician while taking SUSTIVA. ~~Patients should be told that the use of SUSTIVA has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.~~

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breast-feed.** ~~We do~~It is not known if SUSTIVA can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breast-feed because HIV-1 can be passed to the baby in breast milk.

10. **Patient Information**:

a. The third paragraph of the "**What is Sustiva?"** section has been revised as follows:

SUSTIVA does not cure HIV or AIDS~~.~~ and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using SUSTIVA.~~People taking SUSTIVA may still develop other infections and complications. Therefore, it is very important that you stay under the care of your doctor.~~

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

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

b. The third bulleted paragraph in the "**What should I avoid while taking Sustiva?**" section has been revised as follows:

- **Do not breast-feed if you are taking SUSTIVA.** ~~We do~~It is not known if SUSTIVA can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breast-feed because HIV-1 can be passed to the baby in the breast milk. ~~The Centers for Disease Control and Prevention recommend that mothers with HIV not breast-feed because they can pass the HIV through their milk to the baby. Also, SUSTIVA may pass through breast milk and cause serious harm to the baby.~~ Talk with your doctor if you are breast-feeding. You may need to stop breast-feeding or use a different medicine.

c. Victrelis (boceprevir) has been added at the end of the medication list under the "**MEDICINES YOU SHOULD NOT TAKE WITH SUSTIVA/The following medicines may need to be replaced with another medicine when taken with SUSTIVA:**" section.

d. The end section of the **Patient Information** has been revised as follows:

1262274~~A7~~XX Rev ~~June 2012~~Month XXXX
510230013IN~~08~~XX

We have completed our review of these supplemental applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Patient Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible from publicly available labeling repositories.
Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
08/10/2012