CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-360

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
BRAND NAME:	**SUSTIVA™**
GENERIC NAME:	**Efavirenz**
DOSAGE FORM AND STRENGTH:	**300-mg & 600-mg Tablets**
NDA:	**21-360**
TYPE:	**Standard Review**
APPLICANT:	**Bristol-Myers Squibb™**
SUBMISSION DATE:	**30March2001**
OCPB DIVISION:	**DPE III**
ORM DIVISION:	**DAVDP**
OCPB REVIEWER:	**Jennifer L. DiGiacinto, Pharm.D.**
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I. Executive Summary

The Applicant submitted NDA 21-360 on 30March2001 to seek approval for efavirenz (EFV) 300-mg and 600-mg tablets, which is a new formulation for this non-nucleoside reverse transcriptase inhibitor (NNRTI) used in the treatment of HIV-1 infection. The current marketed formulation of EFV is a 50-mg, 100-mg, and 200-mg gelatin capsule formulation. The recommended adult dosage of EFV is 600-mg orally once daily.

A. Recommendations

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant for NDA 21-360 is acceptable.

The Applicant conducted a pivotal bioequivalence (BE) study with the to be marketed EFV tablet formulation (DMP266-108). Both tablet strengths (300-mg and 600-mg) were compared to the current marketed 200-mg capsule and BE was demonstrated.

The data from DMP266-110 demonstrate administration of EFV with a high fat meal increases Cmax and AUC by 79% and 28%, respectively. The increase in Cmax due to administration of EFV with food is greater for the tablet formulation than for the capsule. The increase in other exposure measures (AUCT and AUC∞) is similar for the tablet and capsule formulations.

There may be a relationship between EFV Cmax and CNS adverse events (ADEs) reported by patients. Taking EFV at bedtime may improve the tolerability of CNS ADEs. Therefore, it is recommended that the EFV tablets be taken at bedtime on an empty stomach. The same recommendation is being made for the recent labeling submission (20-972/SLR007) for the EFV capsule.

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) active against HIV-1 infection. EFV is currently available as 50-mg, 100-mg, and 200-mg capsules. The Applicant submits an NDA for SUSTIVA™ tablets (300-mg and 600-mg). The approved adult dose for EFV is 600-mg taken once daily. The new tablet formulation will decrease the pill burden of an EFV containing regimen (1 tablet vs. 3 capsules per dose) and may be more convenient for some patients to take with their other HIV medications. The Applicant

DMP266-108 was the pivotal BE study, which utilized a single-center, open-label, randomized, three-period crossover design to compare the bioequivalence of 300-mg and 600-mg tablet strengths to the 200-mg commercial capsule. Twenty-one healthy volunteers completed the study. The Applicant demonstrated BE for the new tablet formulation of efavirenz (300-mg and 600-mg tablets) when compared to the current marketed efavirenz capsule formulation (200-mg capsule). The 90% CIs for Cmax for the 300-mg and 600-mg tablets were 93%-115% and 99%-123%, respectively. The 90% CIs for AUC for the 300-mg and 600-mg tablets were 96%-108% and 97%-109%, respectively.

The Applicant evaluated the effect of a high-fat meal on EFV exposure, following administration of EFV tablets. DMP266-110 used a single-center, open-label, randomized, two-period crossover design. The subjects (N=22) received a single 600-mg dose of EFV given as a single 600-mg tablet under fasted conditions in one study period and a single 600-mg dose of EFV given as a 600-mg tablet under fed conditions (high-fat/high calorie breakfast meal/ approximately 1000 kcal with 60 grams of fat) in the other study period.

The data from DMP266-110 demonstrate administration of EFV with a high fat meal increases Cmax and AUC by 79% and 28%, respectively. Based on a cross study evaluation, the increase in Cmax due to administration of EFV with food is greater for the tablet formulation than for the capsule. The increase in other exposure measures (AUCT and AUC∞) is similar for the tablet and capsule formulations.

The increase seen in EFV Cmax following administration of EFV tablet in a fed state may be of clinical significance. Data collected in the patients taking the capsule formulation indicate there may be a relationship between high EFV concentrations and CNS ADEs.

The EFV tablet formulation should have the same recommendation for dose administration as the current marketed capsule formulation, which is to be taken at bedtime on an empty stomach. This EFV dosing recommendation is an attempt to avoid the CNS adverse events (ADEs) typically associated with EFV. Taking the tablet at bedtime may make any CNS ADEs more tolerable.

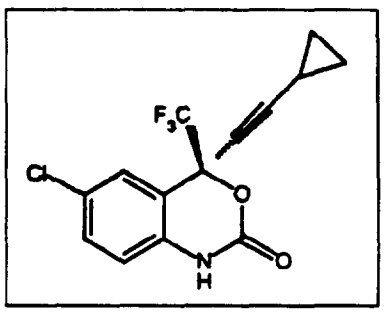
IV. Question-Based Review

A. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Chemical name: (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one

Structure:



Molecular Formula: $C_{14}H_9ClF_3NO_2$

Molecular Weight: 315.68

Formulation: 300-mg (white in color) and 600-mg (yellow in color) film-coated oral tablets

Composition:

INGREDIENT	300-mg Tablet	600-mg Tablet
Efavirenz	300-mg	600-mg
Croscarmellose Sodium NF and Ph. Eur.		
Microcrystalline Cellulose NF and Ph. Eur.		
Sodium Lauryl Sulfate, NF and Ph. Eur.		
Hydroxypropyl Cellulose, LF, NF, and Ph. Eur.		
Lactose, Monohydrate, NF and Ph. Eur.		
Magnesium Stearate, NF and Ph. Eur.		
Opadry™ Yellow		
Opadry™ Clear		
Carnauba Wax NF and Ph. Eur.		
Ink, Purple		
Total		

What is the proposed mechanism of drug action and therapeutic indication?

EFV is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type1 (HIV-1). EFV activity is mediated predominantly by non-competitive inhibition of HIV-1 reverse transcriptase. EFV, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection.

What is the proposed dosage and route of administration?

The proposed dosage regimen for EFV is 600-mg orally once daily. The same regimen is approved for the capsule formulation.

What efficacy, safety, and exposure-response information contributes to the assessment of clinical pharmacology and biopharmaceutics data?

No efficacy data were required for this formulation change and none was submitted. There is no concern about efficacy since the tablet formulations are bioequivalent to the current marketed capsule formulation. Safety data reported for DMP266-110 demonstrated a higher incidence of ADEs when EFV was taken with food compared to the fasted state. CNS symptoms were the most frequent ADEs. The increase seen in Cmax for the EFV tablet during a fed state may be of some clinical significance with regard to subjects experiencing more CNS ADEs. The correlation between EFV plasma concentrations and the development of CNS toxicity is not well defined; however, there may be a relationship between high EFV concentrations and CNS ADEs. The CNS ADEs include dizziness, impaired concentration, depersonalization, abnormal dreams, euphoria, somnolence, amnesia, stupor, agitation, confusion, abnormal thinking, hallucinations, and insomnia.

B. General Biopharmaceutics

What is the *in vivo* relationship of the new EFV tablet formulation compared to the current EFV marketed capsule formulation in terms of comparative exposures?

The EFV proposed commercial tablet formulation (300-mg and 600-mg) is bioequivalent to the current marketed EFV capsule formulation (200-mg).

The Applicant conducted three BE studies (DMP266-054, -058, and –108) comparing tablet formulations to the current approved capsule formulation. The pivotal BE study, DMP266-108 utilized a single-center, open-label, randomized, three-period crossover design to compare the bioequivalence of to-be-marketed 300-mg and 600-mg tablet strengths to the 200-mg commercial capsule. Each subject (N=21) received a single 600-mg dose of all three formulations separated by a 28-day washout period. All formulations were administered to the subjects in a fasted state. Plasma samples were collected out to 504 hours post study drug administration.

BE was demonstrated for the intended EFV commercial tablet formulation (300-mg and 600-mg tablets) compared to the current EFV capsule formulation (200-mg capsule). The 90% CI values for Cmax and AUC fall within the ——— limits, as summarized in Table 1.

Table 1. Pharmacokinetic Parameter Descriptive Statistics, Geometric Mean Ratios, and 90% Confidence Intervals for Efavirenz Tablet Formulation vs. the Efavirenz Capsule Formulation (DMP266-108)

PK Parameter	Statistical Parameter	300-mg Tablet 2 x 300-mg (Test) N=21	600-mg Tablet 1 x 600-mg (Test) N=21	200-mg Capsule 3 x 200-mg (Reference) n=21	GMR Tablet Test/Capsule Reference [90% CI] {% of Reference Mean}	
					300-mg Tablet	600-mg Tablet
Cmax, μM	Mean CV(%)	7.62 29.6	8.06 24.2	7.50 37.4	103.48 [92.73, 115.46]	110.07 [98.65, 122.82]
Tmax, h	Median Range	3.00 —	4.00 —	4.00 —	—	—
AUCT, μM·h	Mean CV(%)	332.57 35.2	338.77 32.9	326.97 34.4	102.38 [96.02, 109.16]	101.94 [95.61, 108.69]
AUC∞, μM·h	Mean CV(%)	363.28 34.3	373.24 32.6	359.01 33.0	101.76 [95.95, 107.92]	102.98 [97.11, 109.22]

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The data from DMP266-110 demonstrate administration of EFV tablets with a high fat meal increases EFV exposure. EFV tablets should be taken on an empty stomach.

In Study DMP266-110, consumption of a high-fat breakfast (approximately 1000 kcal with 60 grams of fat, 60 grams of carbohydrates, and 40 grams of protein) prior to the administration of EFV 600-mg tablet resulted in a significant increase in BA. Geometric mean AUC and Cmax values were approximately 28% and 79% higher under fed conditions (see Table 2). The Agency will recommend that EFV tablets be administered at bedtime on an empty stomach. This recommendation is made because there may be a relationship between high efavirenz concentrations and CNS ADEs. Taking the tablets at bedtime may make any CNS ADEs more tolerable.

Table 2. Pharmacokinetic Parameter Geometric Mean Ratio and 90% CI for Subjects Administered 600-mg Doses of Efavirenz Tablets After a High-Fat/High-Calorie Meal versus Under Fasted Conditions

Pharmacokinetic Parameter	N	Geometric Mean Ratio (% of Ref. Mean)	90% CI (% of Ref. Mean)
Cmax (μM)	22	178.89	158.32, 202.14
C_{24} (μM)	22	115.92	109.65, 122.56
AUCT (μM·h)	22	129.07	123.77, 134.60
AUC∞ (μM·h)	22	127.61	122.28, 133.18

A food effect does exist with the current marketed EFV capsule formulation. Geometric mean AUC and Cmax values were approximately 22% and 39% higher after a high fat meal. Geometric mean AUC and Cmax values were approximately 17% and 51% higher after a low fat/reduced calorie meal. See Appendices for individual study reviews and the pharmacokinetic parameters data.

How do the dissolution conditions and specifications assure *in vivo* performance and quality of the product?

The Applicant and the FDA agreed upon the following dissolution method and specifications:

Dissolution Media: 2% Sodium Lauryl Sulfate in H_2O

Volume: 1000 mL

Temperature: 37° C

Apparatus: 2 (Paddle)

Paddle Speed: 50 rpm

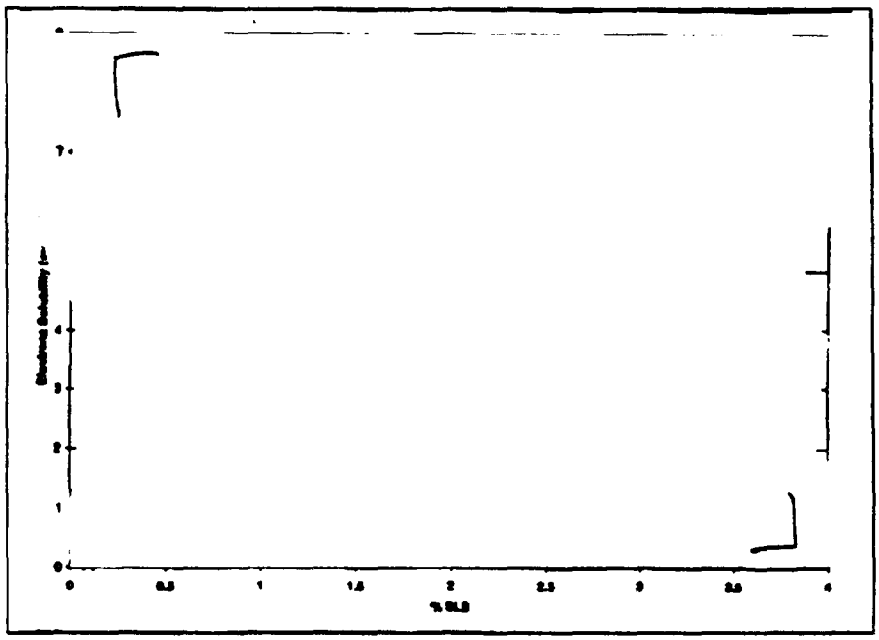
Sinkers: Present

Sampling Times: 10, 15, 30, 45, and 60 minutes

Dissolution Specification: Q = — in 30 minutes

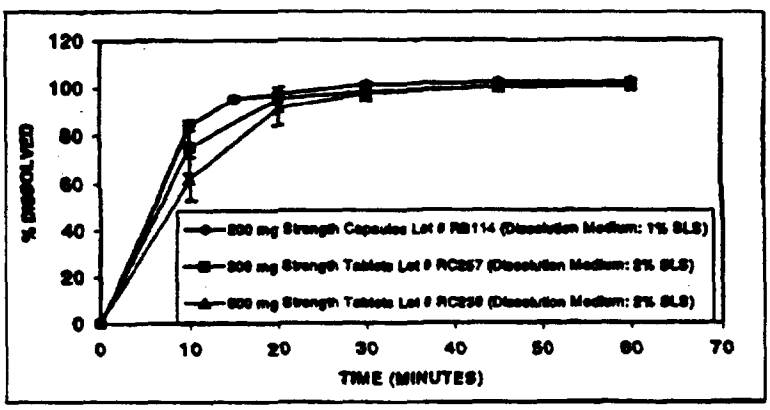
Dissolution of EFV tablets is measured in 1000-mL of water with 2% of sodium lauryl sulfate (SLS) at 37° C. EFV is a hydrophobic compound with a very low solubility in water (approximately 0.009 mg/mL) and a low solubility in the pH range of 1-8. Consequently, 1000 mL of water with 2% SLS was selected as the dissolution medium to ensure that sink conditions are maintained during the testing of both tablet dosage strengths. The surfactant is necessary due to the very low solubility of EFV in the pH range of 1-8. The sinker was added to decrease the variability caused by the sticking of the film coated tablets to different locations inside the vessel.

Figure 1. EFV Solubility vs. SLS Concentration



A comparison of dissolution profiles of the 300-mg and 600-mg tablets (USP Apparatus II with sinkers, 50-rpm, 1000-mL of 2% SLS) and the approved method for the 200-mg commercial capsule (USP Apparatus II with sinkers, 50-rpm 900-mL of 1% SLS) used in the human pivotal BE study DMP266-108 is provided in Figure 2.

Figure 2. Dissolution Profiles of the 300-mg and 600-mg Tablets and the 200-mg Commercial Capsule Evaluated in Study DMP266-108



The dissolution method used for the 300-mg and 600-mg tablets is similar to dissolution method that is accepted by the Agency for the current marketed capsule formulation. The differences are the volume of dissolution medium (1000-mL for tablet compared to 900-mL for the capsule) and the amount of SLS (2% for tablet and 1% for capsule) used. Both changes were made to maintain sink conditions.

Dissolution Profile Data for EFV Capsules, 200-mg, Lot#NJ523 (Clinical Lot #983042)

Test Date & Storage Condition	Vessel No.	Percent Dissolved Time (minutes)				
		10	15	30	45	60
02SEP98 Initial Release						
	1					
	2					
	3					
	4					
	5					
	6					
	Mean	86.3	93.3	96.1	96.8	97.4
	S.D.	1.9	1.7	1.5	1.5	1.6
	RSD%	2.2	1.8	1.6	1.5	1.6
Dissolution Parameters:		USP Paddles (Apparatus 2) at 50 RPM, with a wire sinker around each capsule, 900 mL 1.0% Sodium Lauryl Sulfate at 37 °C.				

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Dissolution Profile Data for EFV Tablets, 300-mg, Lot#PD346 (Clinical Lot#993115)

	Timepoint Percent Dissolved				
Vessel No.	10 minutes	20 minutes	30 minutes	45 minutes	60 minutes
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	83	95	97	99	99
S.D.	11	4	2	1	1
RSD%	14	4	2	1	1

Test Date: 23Apr99

Storage Condition: Initial Release

Dissolution Parameters: USP Paddles (Apparatus 2) at 50 RPM, 1000 mL 2.0% Sodium *Lauryl Sulfate* at 37 °C.

Dissolution Profile for EFV Tablets, 600-mg, Lot # PC302, (Clinical Lot # 993116)

	Timepoint Percent Dissolved				
Vessel No.	10 *minutes*	20 *minutes*	30 *minutes*	45 *minutes*	60 *minutes*
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	80	92	95	97	98
S.D.	11	7	4	3	2
RSD%	13	7	4	3	2

Test Date: 20Apr99

Storage Condition: Initial Release

Dissolution Parameters: USP Paddles (Apparatus 2) at 50 RPM, 1000 mL 2.0% Sodium Lauryl Sulfate at 37 °C.

Conclusion: The Applicant desires a specification of Q = ——— minutes. They did not provide data to support this, however, if in the future they do provide data to support a change to the specification, we will revisit the issue then. The applicant's dissolution method using paddle apparatus with 1000-mL of water with 2% SLS as the dissolution medium at 37° C and a paddle speed of 50 rpm, with sinkers and a specification of Q = — at 30 minutes is acceptable.

C. Analytical Methods

The Applicant measured EFV concentrations in the plasma for study protocol DMP266-108 and DMP266-110 using the validated analytical method ——————— The assay precision and accuracy for calibration standards are summarized below. The lower limit of quantitation was defined as ———————

- The calibration curve and QC sample data from the reported batches indicate that the method met the acceptance criteria for those batches; therefore, the data are acceptable.

/S/ 29 Jan 2002

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Reviewer, Pharmacokinetics, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: /S/ 1-29-02

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V. Labeling Recommendations

CLINICAL PHARMACOLOGY

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

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

PRECAUTIONS

Information for Patients

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

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

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

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DOSAGE AND ADMINISTRATION

Adults: The recommended dosage of SUSTIVA is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that SUSTIVA be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of SUSTIVA with food may lead to an increase in frequency of adverse events (see **CLINICAL PHARMACOLOGY**; ***Effect of Food on Oral Absorption***). Dosing at bedtime improves the tolerability of nervous system symptoms (see **WARNINGS; Nervous System Symptoms, PRECAUTIONS; Information for Patients,** and **ADVERSE REACTIONS**).
Concomitant Antiretroviral Therapy: SUSTIVA must be given in combination with other antiretroviral medications (see **CLINICAL PHARMACOLOGY; Drug Interactions** and **PRECAUTIONS; Drug Interactions and INDICATIONS AND USAGE**).

Pediatric Patients: It is recommended that SUSTIVA be taken on an empty stomach. Table 9 describes the recommended dose of SUSTIVA for pediatric patients 3 years of age or older and weighing between 10 and 40 Kg. The recommended dosage of SUSTIVA for pediatric patients weighing greater than 40 Kg is 600 mg, once daily.

Table 9
Pediatric Dose to be Administered Once Daily

Body Weight		SUSTIVA
Kg	Lbs	Dose (mg)
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

Patient Information

SUSTIVA®* (sus-TEE-vah)
[efavirenz (eh-FAH-vih-rehnz)] capsules and tablets

ALERT: Find out about medicines that should NOT be taken with SUSTIVA.
Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH SUSTIVA."

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

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

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

SUSTIVA does not cure HIV or AIDS. 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

Who should not take SUSTIVA?
Do not take SUSTIVA if you are allergic to the active ingredient, efavirenz, or to any of the inactive ingredients. Your doctor and pharmacist have a list of the inactive ingredients.

What should I avoid while taking SUSTIVA?
- **Women taking SUSTIVA should not become pregnant.** Serious birth defects have been seen in animals treated with SUSTIVA. It is not known whether this could happen in humans. **Tell your doctor right away if you are pregnant.** Also talk with your doctor if you want to become pregnant.
- Women should not rely only on hormone-based birth control, such as pills, injections, or implants, because SUSTIVA may make these contraceptives ineffective. Women must use a reliable form of barrier contraception, such as a condom or diaphragm, even if they also use other methods of birth control.
- **Do not breast-feed if you are taking SUSTIVA.** 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.
- Taking SUSTIVA with alcohol or other medicines causing similar side effects as SUSTIVA, such as drowsiness, may increase those side effects.
- Do not take any other medicines without checking with your doctor. These medicines include prescription and non-prescription medicines and herbal products, especially St John's wort.

Before using SUSTIVA, tell your doctor if you
- **have problems with your liver, or have hepatitis.** Your doctor may want to do tests to check your liver while you take SUSTIVA.
- ***have ever had mental illness or are using drugs or alcohol.***

What important information should I know about taking other medicines with SUSTIVA?
SUSTIVA may change the effect of other medicines, including ones for HIV, and cause serious side effects. Your doctor may change your other medicines or change their doses. Other medicines, including herbal products, may affect SUSTIVA. For this reason, **it is very important to:**
- Let all your doctors and pharmacists know that you take SUSTIVA.
- Tell your doctors and pharmacists about all medicines you take. This includes those you buy over-the-counter and herbal or natural remedies.

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

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

MEDICINES YOU SHOULD NOT TAKE WITH SUSTIVA
The following medicines may cause serious and
life-threatening side effects when taken with SUSTIVA. You should not take any of these medicines while taking SUSTIVA**:
- Hismanal® (astemizole)
- Propulsid® (cisapride)
- Versed® (midazolam)
- Halcion® (triazolam)
- Ergot medications (for example, Wigraine® and Cafergot®)

The following medicines may need to be replaced with another medicine when taken with SUSTIVA**:
- Fortovase®, Invirase® (saquinavir)
- Biaxin® (clarithromycin)

The following medicines may need to have their dose changed when taken with SUSTIVA**:
- Crixivan® (indinavir)
- Mycobutin® (rifabutin)
- Methadone

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

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

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

Keep SUSTIVA out of the reach of children.

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

* SUSTIVA® is a registered trademark of Bristol-Myers Squibb Pharma Company.
** The brands listed are the registered trademarks of their respective owners and are not trademarks of Bristol-Myers Squibb Company.

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Princeton, NJ 08543 USA

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VI. Appendices (Filing Form and Individual Study Reviews)

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-360	Brand Name	SUSTIVA™
OCPB Division (I, II, III)	III	Generic Name	Efavirenz
Medical Division	Antivirals	Drug Class	Non-Nucleoside Reverse Transcriptase Inhibitor
OCPB Reviewer	Jennifer L. DiGiacinto, Pharm.D.	Indication(s)	HIV-1 Infection
OCPB Team Leader	Kellie S. Reynolds, Pharm.D.	Dosage Form	300-mg and 600-mg tablets
		Dosing Regimen	Adults: 600-mg each day
Date of Submission	03/30/01	Route of Administration	oral
Estimated Due Date of OCPB Review	01/16/02	Sponsor	Bristol-Myers-Squibb™
PDUFA Due Date		Priority Classification	1S
Division Due Dates			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
1. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
Fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
Alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
Traditional design; single / multi dose:	x	3	3	
Replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted] x	4	4	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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Bioequivalence Studies:

Background
The first BE study, DMP266-054, is a pilot study conducted with a 300-mg tablet and comparing it to the current marketed 200-mg capsule formulation. The second BE study, DMP266-058, is a study conducted with both 300-mg and 600-mg tablets and comparing those to the 200-mg capsule. In this study, Cmax failed the 90% CI ——— criteria for both strengths. Consequently, the tablet formulation was modified and the new formulation was used in the third BE study, DMP266-108. Both strengths (300-mg and 600-mg) were compared to the 200-mg capsule and BE was demonstrated.

This review will provide a brief report for the first two BE studies (DMP266-054, -058) and a full report for DMP266-108, which studied the 'to-be-marketed' EFV tablet formulations.

DMP266-054
A Phase I, Single-Dose, Open-Label, Two-Period, Crossover Pilot Bioavailability Study in Healthy Volunteers Comparing Efavirenz Tablets (Formulation ————) to the Efavirenz Capsules

Investigator, Study Site, and Study Dates
- ————————
- ————————
- 16January1999 – 13Febuary1999

Study Description
DMP266-054 was a pilot study that used a single-center, open-label, randomized, two-period crossover design to compare the bioequivalence of a potential 300-mg tablet to the 200-mg commercial capsule. Twelve healthy volunteers completed the study. Each subject received a single 600-mg dose of both formulations separated by a 14-day washout period. Both formulations were administered to the subjects in a fasted state. Plasma samples were collected out to 336 hours post study drug administration.

Study Drug Formulations
- 300-mg tablet (Formulation ————), Lot # 983073
- 200-mg commercial capsule, Lot # 983042

Study Results

Pharmacokinetic Parameter Descriptive Statistics, Geometric Mean Ratios, and 90% Confidence Intervals for Efavirenz Tablet Formulation vs. the Efavirenz Capsule Formulation (DMP266-054)

PK Parameter	N	Tablet Mean (CV%)	Capsule Mean (CV%)	GMR (% of Reference Mean)	90% CI (% of Reference Mean)
Cmax, μM	12	8.19 (26.3)	8.34 (31.5)	99.70	84.68, 117.38
AUCT, μM·h	12	289.0 (28.6)	297.3 (25.3)	96.31	88.74, 104.53
AUC∞, μM·h	12	317.9 (28.8)	329.4 (26.2)	95.70	89.21, 102.67

Reviewer Note: *Since the washout period between the two formulations was only 14-days in length and EFV single dose half-life can be up to 80 hours, the Applicant anticipated some residual drug would be present in the pre-dose samples following the washout period. Six subjects had residual drug present and corrections were made to account for this residual drug prior to any BE analysis. In order to alleviate this, the Applicant lengthened the washout period in the subsequent BE studies to 28 days.*

Assessment/Conclusion

Bioequivalence was demonstrated in DMP266-054 for the newly formulated 300-mg EFV tablet when compared to the current marketed 200-mg EFV capsule. The Applicant conducted another BE study (DMP266-058) enrolling more subjects and comparing both tablet strengths for EFV (300-mg and 600-mg) to the 200-mg EFV capsule.

DMP266-058

A Phase I, Open-Label, Single-Dose, Three-Period Crossover Bioavailability Study in Healthy Volunteers Comparing 300-mg and 600-mg Efavirenz Tablets to Efavirenz Capsules.

Investigator, Study Site, and Study Dates

- [redacted]
- [redacted]
- 12June1999 – 28August1999

Study Description

DMP266-058 utilized a single-center, open-label, randomized, three-period crossover design to compare the bioequivalence of potential 300-mg and 600-mg tablets to the 200-mg commercial capsule. Twenty-eight healthy volunteers completed all three periods of the study and are included in the pharmacokinetic analysis. Each subject received a single 600-mg dose of all 3 formulations separated by a 28-day washout period. All formulations were administered to the subjects in a fasted state. Plasma samples were collected out to 504 hours post study drug administration.

Study Drug Formulations

- 300-mg tablet (Formulation [redacted], Lot # 993115
- 600-mg tablet (Formulation [redacted], Lot#993116
- 200-mg commercial capsule, Lot # 983042

Study Results

Pharmacokinetic Parameter Descriptive Statistics, Geometric Mean Ratios, and 90% Confidence Intervals for Efavirenz Tablet Formulation versus the Efavirenz Capsule Formulation (DMP266-058)

PK Parameter	EFV Formulation	N	Tablet Arith. Mean (CV%)	Capsule Arith. Mean (CV%)	GMR (% of Reference Mean)	90% CI (% of Reference Mean)
Cmax, µM	300-mg tablet	28	9.51 (23.3)	7.58 (29.2)	123.35	113.38, 134.21
	600-mg tablet	28	9.17 (28.7)	7.58 (29.2)	118.38	108.80, 128.79
AUCT, µM·h	300-mg tablet	28	427.64 (38.8)	387.45 (44.5)	110.97	105.64, 116.56
	600-mg tablet	28	419.01 (42.2)	387.45 (44.5)	107.62	102.46, 113.05
AUC∞, µM·h	300-mg tablet	28	463.18 (38.6)	421.85 (41.6)	109.82	104.94, 114.92
	600-mg tablet	28	451.41 (40.8)	421.85 (41.6)	106.61	101.88, 111.57

Assessment/Conclusion
The Applicant failed to demonstrate BE in DMP266-058. Cmax for both tablet strengths did not meet the 90% CI of [redacted] The Applicant indicates the increased Cmax was related to the amount of [redacted] within the tablet formulations [redacted] Therefore, the Applicant modified the formulations by [redacted] the [redacted] to [redacted] The Applicant conducted a BE study with the modified EFV tablet formulation (DMP26-108).

DMP266-108 (Pivotal BE Study)
A Phase I, Open-Label, Single-Dose, Three-Period Crossover Bioavailability Study in Healthy Volunteers Comparing 300-mg (Formulation [redacted] and 600-mg (Formulation [redacted]) Efavirenz Tablets to Efavirenz Capsules

Investigator, Study Site, and Study Dates
- [redacted]
- [redacted]
- 17June2000 – 15September2000

Study Description
DMP266-108 utilized a single-center, open-label, randomized, three-period crossover design to compare the bioequivalence of modified 300-mg and 600-mg tablet strengths to the 200-mg commercial capsule. Twenty-one healthy volunteers completed the study. Each subject received a single 600-mg dose of all three formulations separated by a 28-day washout period. All formulations were administered to the subjects in a fasted state. Plasma samples were collected out to 504 hours post study drug administration.

Study Drug Formulations
- 300-mg tablet (Formulation [redacted] , Lot # 003222 600-mg tablet (Formulation [redacted]), Lot # 003223
- 200-mg commercial capsule, Lot # 003237

Pharmacokinetic Sample Times
- Blood samples to measure efavirenz plasma concentrations were obtained prior to dosing (0 hour) on Day 1 of each period and at 1, 2, 3, 4, 5, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 336, and 504 hours post dose administration

Pharmacokinetic Parameters

- Cmax- Observed maximum plasma concentration
- C_{24} – Observed plasma concentration at 24 hours
- AUCT- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration-time point, calculated by linear trapezoidal rule
- AUC∞ - Area under the plasma concentration-time curve from time zero to time infinity; calculated as AUCT + $C_{last}/\lambda n$, where C_{last} is the last quantifiable concentration
- ke: Terminal or disposition rate constant; calculated as the negative slope (by linear regression) of the terminal natural log (ln)-linear portion of the plasma concentration-time curve
- t½ : Terminal or disposition half-life; calculated as 0.693/ke
- Clo: Apparent oral clearance; calculated as dose/AUC∞

DMP266-108 Assay Validation

The Applicant measured EFV concentrations in the plasma for study protocol DMP266-108 using the validated analytical method of ———————— The inter-assay precision and accuracy for calibration standards are summarized below. The lower limit of quantitation was defined as ————

- The calibration curve and QC sample data from the reported batches indicate that the method met the acceptance criteria for those batches.

Study Results

Pharmacokinetic Parameter Descriptive Statistics, Geometric Mean Ratios, and 90% Confidence Intervals for Efavirenz Tablet Formulation vs. the Efavirenz Capsule Formulation (DMP266-108)

PK Parameter	Statistical Parameter	300-mg Tablet 2 x 300-mg (Test) N=21	600-mg Tablet 1 x 600-mg (Test) N=21	200-mg Capsule 3 x 200-mg (Reference) n=21	GMR Tablet Test/Capsule Reference [90% CI] (% of Reference Mean)	
					300-mg Tablet	600-mg Tablet
Cmax, µM	Mean CV(%)	7.62 29.6	8.06 24.2	7.50 37.4	103.48 [92.73, 115.46]	110.07 [98.65, 122.82]
Tmax, h	Median Range	3.00	4.00	4.00	----------	----------
AUCT, µM·h	Mean CV(%)	332.57 35.2	338.77 32.9	326.97 34.4	102.38 [96.02, 109.16]	101.94 [95.61, 108.69]
AUC∞, µM·h	Mean CV(%)	363.28 34.3	373.24 32.6	359.01 33.0	101.76 [95.95, 107.92]	102.98 [97.11, 109.22]
ke, h^{-1}	Mean CV(%)	0.0091 37.1	0.0089 35.1	0.0091 38.7		
t½, h	Mean CV(%)	76.03 37.4	78.21 35.5	75.81 39.0		
CL_{0ral}, L/hr	Mean CV(%)	5.78 31.2	5.59 31.0	5.88 35.2		

Reviewer Note: *The modification to the EFV tablet formulation [redacted] was sufficient for both tablet strengths to meet the BE criteria when compared to the 200-mg capsules. The Applicant has determined this formulation to be the 'to be marketed' formulation for EFV tablets.*

Assessment/Conclusion

The Applicant demonstrated BE for the new tablet formulation of EFV (300-mg and 600-mg tablets) when compared to the current marketed EFV capsule formulation (200-mg capsule).

DMP266-110

Title
A Phase I, Open-Label, Single-Dose, Randomized, Two-Period Crossover Study in Healthy Volunteers to Determine the Effect of Food on the Bioavailability of Efavirenz Tablets.

Investigator/Study Site/ Study Dates
- [redacted]
- [redacted]
- 28April2001 – 28August2001

Study Description
This study used a single-center, open-label, randomized, two-period crossover design. The subjects received a single 600-mg dose of EFV given as a single 600-mg tablet under fasted conditions in one study period and a single 600-mg dose of EFV given as a 600-mg tablet under fed conditions (high-fat/high calorie breakfast meal/ approximately 1000 kcal with 60 grams of fat) in the other study period. A 28-day minimum washout period separated study periods. Serial plasma samples were obtained over a 504-hour (21-days) interval after each single dose administration. Twenty-two subjects completed both periods (24 subjects initially enrolled) and are included in the pharmacokinetic analysis. Two subjects discontinued from the study.

Study Drug
- Efavirenz 600-mg tablets - Lot #003223 (Same lot # used in the bioequivalence study DMP266-108)

Pharmacokinetic Parameters
- Cmax- Observed maximum plasma concentration
- C_{24} – Observed plasma concentration at 24 hours
- AUCT- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration-time point, calculated by linear trapezoidal rule
- AUC∞ - Area under the plasma concentration-time curve from time zero to time infinity; calculated as AUCT + $C_{last}/\lambda n$, where C_{last} is the last quantifiable concentration

DMP266 Assay

The Applicant measured EFV concentrations in the plasma for study protocol DMP266-110 using the validated analytical method of [redacted] The inter-assay precision and accuracy for calibration standards are summarized below. The lower limit of quantitation was defined as [redacted]

- The calibration curve and QC sample data from the reported batches indicate that the method met the acceptance criteria for those batches.

Study Results

Pharmacokinetic Parameter Geometric Mean Ratio and 90% CI for Subjects Administered 600-mg Doses of Efavirenz After a High-Fat/High-Calorie Meal Compared to Under Fasted Conditions

Pharmacokinetic Parameter	N	Geometric Mean Ratio (% of Ref. Mean)	90% CI (% of Ref. Mean)
Cmax (μM)	22	178.89	158.32, 202.14
C_{24} (μM)	22	115.92	109.65, 122.56
AUCT (μM·h)	22	129.07	123.77, 134.60
AUC∞ (μM·h)	22	127.61	122.28, 133.18

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DMP266-057 is the food effect study conducted with the current marketed capsule formulation.

Food Effect Study Results Comparison (DMP266-057 vs. DMP266-110 [Fed and Fasted States])

Study	N	Cmax Fed μM Mean (CV%)	AUCT Fed μM·h Mean (CV%)	AUC∞ Fed μM·h Mean (CV%)	Cmax Fasted μM Mean (CV%)	AUCT Fasted μM·h Mean (CV%)	AUC∞ Fasted μM·h Mean (CV%)	GM Ratio of Fed vs. Fasted (% of Ref. Mean) [90% CI] (% of Ref. Mean) Cmax	AUCT	AUC∞
DMP266-057 Capsule	18	9.30 (13.5)	404 (28.3)	444 (30.4)	6.92 (23)	324 (28.7)	371 (29.4)	139 [124, 155]	127 [122, 131]	122 [117, 128]
DMP266-110 Tablet	22	12.25 (26.3)	370 (24.8)	397 (23.7)	6.90 (30.5)	289 (28.5)	313 (26.4)	179 [158, 202]	129 [124, 135]	128 [122, 133]

Reviewer Note: The Cmax value for DMP266-110 (tablet formulation) is higher than what is seen in DMP266-057 (approved capsule formulation) during a fed state. The other pharmacokinetic parameters seem to be similar between formulations in both the fed and fasted states. This increase in Cmax may be of some clinical significance with regard to subjects experiencing more CNS adverse effects. In study DMP266-057, the Applicant also looked at EFV administered with a reduced-fat/low-calorie meal. Interestingly, the Cmax for the reduced-fat fed state was larger than what was demonstrated with the high-fat fed state (Geometric Means [90% CI]: high-fat = 139 [124, 155] and reduced fat = 151, [135, 168]). This creates some concern for the tablet if a further increase in the Cmax occurs when a reduced-fat/low calorie meal is administered.

Assessment/Conclusion

The food effect study is acceptable. The current label for EFV capsule states that EFV should be administered at bedtime on an empty stomach. There may be a relationship between high EFV concentrations and CNS adverse events (ADEs) and this EFV dosing recommendation is an attempt to avoid the CNS ADEs typically associated with EFV. Taking EFV at bedtime may make any CNS ADEs more tolerable.

The data from DMP266-110 demonstrate that a food effect does exist with the new tablet formulation. Additionally, the tablet formulation seems to have a larger increase in Cmax during a high-fat/high calorie fed state than what is seen with the marketed capsule formulation.

The EFV tablet formulations should have the same recommendation for dose administration as the current marketed capsule formulation. In addition, the Applicant may want to study the effects of administering EFV at different times after a meal. This would provide useful data for determining at what time the food effect with EFV diminishes and; therefore, allow more detailed instructions on EFV dosing for the patients.

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

/s/

Jennifer DiGiacinto
1/31/02 10:24:27 AM
BIOPHARMACEUTICS

Kellie Reynolds
2/22/02 12:18:00 PM
BIOPHARMACEUTICS

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