

GROUP LEADER MEMORANDUM

NDA: 20-972

Drug and Indication: Sustiva™ (efavirenz capsules) for treatment of HIV-1 infection

Dose: 600 mg once daily

Applicant: DuPont Pharmaceuticals

Submission received: June 11, 1998

Date draft review completed: September 10, 1998

Date of Memorandum: September 17, 1998

The applicant has requested approval for a non-nucleoside reverse transcriptase inhibitor, Sustiva™ (efavirenz capsules) for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents, under accelerated approval regulation, 21 CFR 314 subpart H. This indication is based on surrogate endpoint analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies up to 24 weeks in duration.

In support of the request for accelerated approval, the applicant has submitted the 24-week surrogate endpoint data from subgroup of 928 patients from three ongoing controlled clinical trials. Two of these trials will provide data to support traditional approval. The applicant has also submitted 12-week surrogate endpoint data from one ongoing trial in 57 pediatric patients ages 3 to 16 years. The primary efficacy measure was the percent of patients with plasma HIV RNA <400 copies/mL (<500 copies/mL in ACTG study) using approved Amplicor™ Monitor assay. Data from 21 phase I pharmacokinetic and drug interaction studies and six phase II studies were also submitted in support of the application.

A total of 2215 patients received efavirenz at various doses across all studies and are included in the safety database. Approximately 970 patients received efavirenz at a dose of 600mg QD for at least 24 weeks. Safety experience was also supported by reported adverse events from phase I/II trials and the expanded access program.

I am in agreement with the conclusions of the primary medical reviewer that data in this application support the conclusion that efavirenz in combination with other antiretroviral agents provides meaningful therapeutic benefit over available therapies. Therefore, this new drug application should be approved under the accelerated approval regulation. Two 48-week trials

evaluating effects of efavirenz on long-term suppression of HIV RNA are underway.

The following issues warrant comment at the time of this regulatory action:

1. Safety

The most concerning adverse events associated with efavirenz therapy were CNS symptoms and skin rash.

In addition to central nervous system symptoms of dizziness, psychiatric symptoms including, but not limited to, somnolence, impaired concentration, abnormal dreams, and insomnia, were reported in 50% patients receiving efavirenz. These symptoms were severe in 2.6% of patients who received efavirenz 600 mg and in 1.4% of patients receiving control regimens. In clinical trials 2.6% of patients discontinued therapy because of nervous system symptoms. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks. Efavirenz should be used with caution in patients with a history of a pre-existing psychiatric disorder or drug abuse. Dosing at bedtime may improve the tolerability of these symptoms.

Skin rash was reported by 27% of adult patients treated with 600 mg of efavirenz compared with 17% of patients in the control group. In clinical trials, one patient developed erythema multiforme and another Stevens-Johnson syndrome. The incidence of rash and severity of rash was much more pronounced in the pediatric population. Rash was reported by 40% of children treated with efavirenz. Five patients discontinued treatment because of rash.

2. Teratogenic Effect

Fetal malformations (anophthalmia, microphthalmia, and cleft palate) have been observed in three of 20 fetuses/infants from efavirenz treated cynomolgus monkeys in a developmental toxicity study. The pregnant monkeys had plasma drug concentrations similar to those in humans dosed with 600 mg of efavirenz. Because teratogenic effects have been seen in primates at efavirenz exposures similar to those in humans at the proposed marketed dose, pregnancy should be avoided in women receiving efavirenz. There is no safety experience of efavirenz in pregnant women. Efavirenz should be used during pregnancy only in women without other therapeutic options.

3. Clinical Trial Design

Study 006 is an ongoing, open-label, randomized trial of efavirenz/zidovudine/lamivudine compared to indinavir/zidovudine/lamivudine or efavirenz/indinavir in 450 HIV-infected treatment-naive patients.

Number of patients with HIV RNA - Week 24

	HIV RNA <400**	HIV RNA >400	Discontinuation*
EFV/ZDV/LAM	109 (71%)	6 (4%)	39 (25%)
IDV/ZDV/LAM	82 (55%)	10 (7%)	56 (38%)
EFV/IDV	93 (63%)	15 (10%)	40 (27%)

*includes patients who dropped out of the study and/or did not have a 24 week HIVRNA measured

**non completer=failure analysis

More patients on IDV/ZDV/LAM discontinued study treatment prior to 24 weeks compared to the other two treatment arms. The differences in discontinuation rates were predominantly the result of adverse events in the IDV/ZDV/LAM arm. These patients were counted as virologic failures (HIV RNA \geq 400 copies/mL). Therefore, discontinuations accounted for a substantial fraction of the differences in the percent below 400 copies/mL. It is difficult to assess the relative efficacy of the treatment arms given disproportional discontinuation in this open-label study. It appears that superiority may be due to early discontinuations in the control arm. However, efavirenz containing arms certainly demonstrated efficacy comparable to the control arm.

Study 020 is an ongoing, randomized, double-blind, placebo-controlled trial of 24 weeks of therapy comparing efavirenz/IDV/NRTIs to placebo/IDV/NRTIs in 282/330 HIV-infected patients who were NRTI-experienced, NNRTI and PI treatment-naive. Physicians were allowed to add up to two NRTIs of their choice to the treatment regimen of EFV/IDV or placebo/IDV.

Percent of patients with HIV RNA <400 copies/mL - Week 24

	EFV/IDV/NRTIs	IDV/NRTIs	p-value
HIV RNA <400*	58% (79/136)	50% (73/146)	0.19

*non completer=failure analysis

There was no significant difference between the two treatment arms in the percent of patients achieving plasma RNA levels < 400 copies/mL at week 24 of treatment. A significant difference was seen when an investigational assay with a lower limit of quantification of 50 copies/mL was used.

ACTG 364 is an ongoing 48-week double-blind, placebo-controlled trial in NRTI-experienced patients who had completed two prior ACTG studies. Twenty four week viral RNA data for a subgroup of 196 patients were provided in the NDA. One treatment group received efavirenz in combination with nelfinavir (NFV) and two NRTIs, and the other group received NFV and two NRTIs.

CD 4 cell count and percent of patients with HIV RNA <500 copies/mL - Week 24

	NFV+ 2 NRTIs	EFV + 2 NRTIs 97.5%CI	EFV+NFV+ 2NRTIs p-value
HIV RNA <500*	44% (29/66)	58.5% (38/65) -5%, 34%	73% (46/64) 0.002
CD4 count	+69	+80	+47

*non completer=failure analysis

Based on the proportion of patients with HIV RNA counts below 500 copies/mL at 24 weeks of treatment, the 4 drug treatment arm (EFV+NFV+2NRTIs) was superior to the 3 drug arm (NFV+2NRTIs). Efavirenz in combination with two NRTIs was equivalent to NFV+2NRTIs with a lower bound CI of -5%. The CD4 cell response from baseline was smaller in the four drug regimen than in the other comparison groups. This seems unlikely to represent an adverse effect of efavirenz on CD4. The magnitude of these differences was not large and these differences were not observed in other trials.

ACTG 382 (Pediatric)

Fifty seven patients, 3 to 16 years of age were enrolled into this 48-week, ongoing trial designed to evaluate the safety, tolerability and antiviral activity of efavirenz in combination with nelfinavir. All children were NRTI-experienced and are permitted to use concomitant NRTIs. The applicant provided viral RNA data for 48 patients at week 12 and 20 patients at week 20 of treatment. At week 12, 67% of patients had plasma HIV RNA levels <400 copies/mL. These data are supportive of the efficacy of efavirenz in the treatment of HIV-1 infection when used in combination with other antiretroviral agents.

Because of the high incidence of rash in children taking efavirenz, further study of the incidence of rash in children and its correlation with plasma efavirenz concentrations is warranted.

4. Dose Selection

The proposed dose for efavirenz is 600 mg once daily. It was estimated that total plasma concentrations of efavirenz needed to exceed the IC₉₀ for viral variants containing the K103N RT substitution range from 3.5 μ M to 7.0 μ M. A higher percentage of patients who received the 600 mg dose achieved a trough level exceeding 3.5 or 7.0 μ M compared to patients receiving 400 or 200 mg of efavirenz. In a dose ranging clinical study (005), efavirenz 200 mg, 400 mg, and 600 mg appeared to be comparable across the treatment arms in the effect on the proportion of patients with HIV RNA below 400 copies/mL at week 16 of treatment. This issue was discussed with the applicant on many occasions, however, a strong argument was provided by the company that the 600 mg efavirenz dose is supported by both clinical trials and by in vitro resistance data (see NDA, vol.1, item 3).

5. Labeling Discussions

Substantive labeling issues to be resolved at the time of this memo include the following:

(b)(4)(CC)-----

Proposed Phase IV Commitments

1. Chemistry

Once the first ten scale up batches of SP234 and SD573 have been accomplished, please (b)(4)(CC)---he specification limits for drug substance and (b)(4)(CC)-----

2. Microbiology

(b)(4)(CC)-----

3. Pharmacology/Toxicology

Please complete the ongoing (b)(4)(CC)-----d report the results in a timely manner.

4. Clinical Pharmacology/Biopharmaceutics

Please complete th(b)(4)(CC)-----

Please conduct a (b)(4)(CC)-----

5. Clinical

(b)(4)(CC)-----

Please establish a v(b)(4)(CC)-----
launch.

Please continue your p(b)(4)(CC)-----
along with obtaining -----

Stanka Kukich, M.D.
Acting Medical Team Leader, HFD-530

cc:
NDA 20-972
HFD-530/HJolson/HHaverkos/SKukich