DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JUL 18 2000

Patricia Dewalt, Ph.D.
Director, Regulatory Affairs
DuPont Pharmaceuticals Company
Chestnut Run Plaza, Maple Run
974 Centre Road
Wilmington, DE 19805

RE: NDA 20-972
Sustiva (efavirenz) capsules
MACMIS ID #8971

Dear Dr. Dewalt:

This letter is to inform the Regulatory Affairs Department of DuPont Pharmaceuticals Company (DuPont) that disseminated advertisements for Sustiva are in violation of the Federal Food, Drug and Cosmetic Act (the Act) and its applicable regulations. As part of our monitoring and surveillance program, the Division of Drug Marketing, Advertising and Communications (DDMAC) reviewed the following advertisements submitted on Form FDA 2253:

1. the professional advertisement titled "Sustiva achieves a major milestone...So life goes on"
2. the consumer advertisement titled "Powerful therapy that fits the way you live...So life goes on"
3. the professional advertisement titled "Extending the limits of power and tolerability...So life goes on"

These advertisements violate the Act for the reasons cited below.

Misleading claims

The claim "...So Life Goes On" is misleading because it broadens the indication for Sustiva by implying that it improves survival in patients with HIV infection. The approved product labeling (PI) for Sustiva includes data on HIV viral suppression for up to 112 weeks. However, Sustiva's impact on improving survival in patients with HIV has not been demonstrated by substantial evidence.

Your claim that Sustiva is "Establishing a New Standard of Care" is misleading because it overstates the role of Sustiva in HIV therapy. To support this claim, you reference the Department of Health and Human Services (DHHS) guidelines. The claim implies that Sustiva alone is a standard of care and misrepresents the current DHHS guidelines. Sustiva monotherapy is not recommended as a standard of care. Sustiva is listed as one of several drugs that may be included in "strongly preferred" combination drug regimens for therapy-naïve patients with established HIV infection. The referenced DHHS guidelines list preferred combination regimens but do not identify individual drugs as standards of care.

The claim "In one study, Sustiva kept it [HIV virus] at those levels for more than two years" is misleading because it implies that Sustiva may be used as monotherapy. The claim attributes the lowering of HIV virus to undetectable levels to Sustiva alone. The PI states that Sustiva must be taken in combination with other antiretroviral therapies and that resistance rapidly emerges with monotherapy. Presentation of a previous statement describing "combination therapies containing Sustiva" does not sufficiently correct the misleading implication.

DuPont presents a claim that Sustiva's "Pharmacologic properties may minimize resistance." To support this claim, DuPont presents the statements "40-55 hour half-life with trough levels 26-fold > IC_{90} for wild type isolates" and "Penetrates the CSF and lymph nodes." This presentation is misleading because the clinical significance of penetration into the lymph nodes or cerebral spinal fluid (CSF) is not known and has not been shown to impact resistance. Furthermore, the impact of a long drug half-life on resistance is not known. Finally, this presentation is inconsistent with the PI which states that "resistant virus emerges rapidly when efavirenz is administered as monotherapy" and "HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in IC_{90}) compared to baseline can emerge *in vitro*."

Claims regarding the effectiveness of Sustiva in patients with high baseline viral loads are misleading because they overstate the known efficacy of Sustiva. You claim that regimens including Sustiva achieve "sustained viral load suppression to < 50 copies/mL in patients with high baseline viral loads." However, the clinical study cited (Study 006) was not designed to assess the impact of Sustiva in combination with other antiretroviral therapy in patients with high baseline viral loads (defined in Study 006 as > 100,000 copies/mL). Subset analysis of Study 006 is inadequate to support such a claim.

Statements that Sustiva "fits the way you live" or offers "convenient" dosing are misleading. The Sustiva PI recommends bedtime dosing during the first two to four weeks "to improve the tolerability of nervous system side effects" and that Sustiva should not be taken with high fat meals. Failing to provide this context with your "convenience" claims misleadingly implies that Sustiva can be taken without restrictions.

Unsubstantiated Superiority Claims
Claims that imply that combination therapies containing Sustiva are superior to all protease inhibitor-containing regimens are misleading because Sustiva's superiority in combination regimens has not been established by substantial evidence. For example, DuPont claims that Sustiva is "superior to protease-inhibitor containing regimens for naïve or NRTI-experienced patients." However, of the approved protease inhibitors, Sustiva has been compared to only two of six in head-to-head trials.

The claim that Sustiva has "...fewer gastrointestinal (GI) side effects, such as nausea, vomiting and diarrhea, than Viracept" is misleading because it is an unsubstantiated superiority claim. The ACTG 364 trial was not designed to assess the incidence of adverse drug reactions. Furthermore, the data from the ACTG 364 trial demonstrated that a similar incidence of GI adverse effects occurred in the compared treatment arms. While diarrhea did occur more frequently in the Viracept arm (9% versus 3%), the incidence of nausea and vomiting were the same per the Sustiva PI.

Fair Balance
All three advertisements lack fair balance because the risk information presented is inadequate. Contraindications to Sustiva therapy are not included and common adverse reactions (e.g., rash) are omitted. For example, the "Milestone" advertisement presents numerous efficacy claims, but minimal risk information. Neither contraindications nor common adverse effects are presented. In addition, the risk of central nervous system (CNS) effects is minimized by stating that "In a small number of patients, serious psychiatric adverse experiences have been reported" because 53% of patients taking Sustiva report a range of CNS effects.

Requested Action
DuPont should immediately discontinue these print advertisements and all other promotional materials for Sustiva that contain the same or similar claims or presentations. We request that DuPont respond, in writing, with its intent to comply with the above. DDMAC should receive DuPont's written response no later than August 1, 2000. This response should list similarly violative materials with a description of the method for discontinuation and the discontinuation date.

If you have any questions, please contact the undersigned by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all

future correspondence regarding this matter, please refer to MACMIS ID #8971 and the NDA number. DDMAC reminds DuPont that only written communications are considered official.

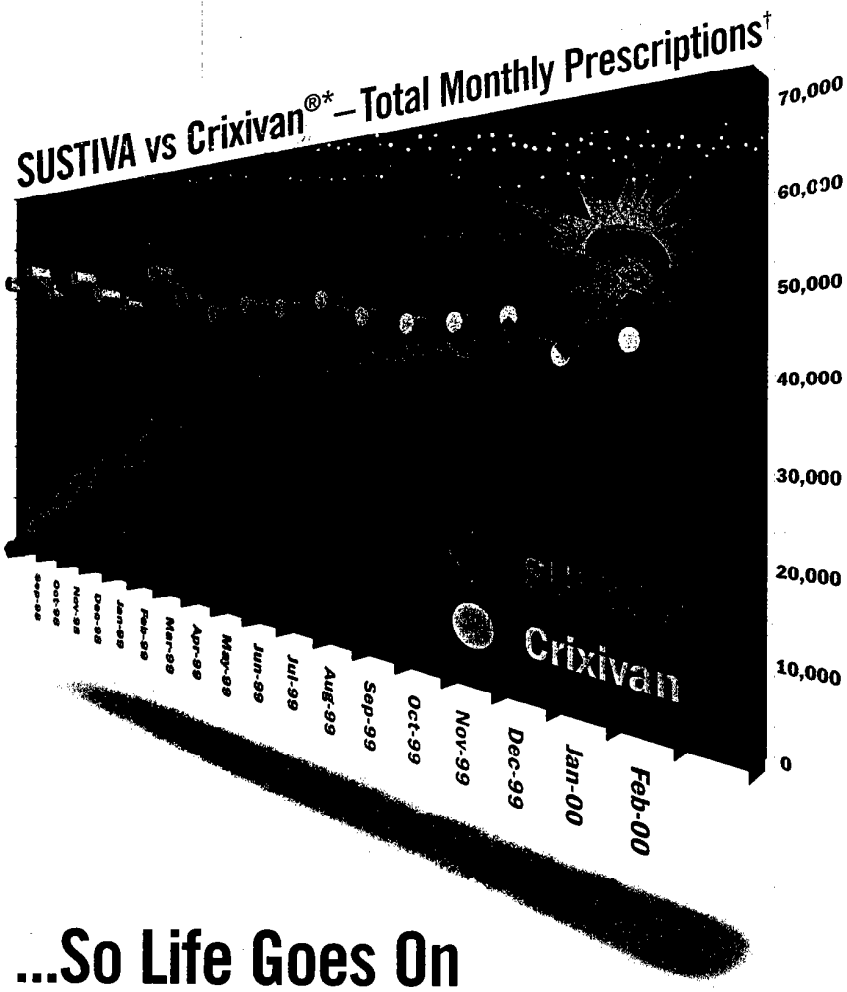
Sincerely,

/S/

Rebecca Redman, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

A shifting trend
in HIV/AIDS treatment

SUSTIVA achieves a major milestone



Reaching More Patients Than Crixivan,
Establishing a New Standard of Care[1]

...So Life Goes On

Once Daily
SUSTIVA™
efavirenz

In a small number of patients, serious psychiatric adverse experiences have been reported. Patients with serious psychiatric experiences should contact their physician immediately to discuss their therapy. Women should not become pregnant while taking SUSTIVA because birth defects have been seen in cynomolgus monkeys given SUSTIVA.

[1] *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents.* Department of Health and Human Services, January 2000. SUSTIVA is the only NNRTI listed as part of a "strongly recommended" regimen for initial treatment.

*Crixivan is a registered trademark of Merck & Co.

†IMS National Prescription Audit.

DUPONT®
DuPont Pharmaceuticals Company

Printed in U.S.A.

For further information visit our website at www.sustiva.com or call 1-800-4-PHARMA (1-800-474-2762).
Please see brief summary of complete Prescribing Information for SUSTIVA on following page.

Powerful Therapy That Fits the Way You Live

LOWER VIRUS LEVELS—LONGER

SUSTIVA isn't just effective in combination treatment of HIV-1 infection; it's effective long-term. In clinical studies, combination therapies containing SUSTIVA were proven superior to protease inhibitor–containing regimens in lowering the HIV virus to levels that were undetectable.[1] In one study, SUSTIVA kept it at those levels for more than two years.[2]

TAKE IT JUST ONCE A DAY

SUSTIVA fits the way you live because you take it just once a day. It can be taken with or without meals, and there's no need to drink lots of liquid.

GENERALLY TOLERABLE SIDE EFFECTS

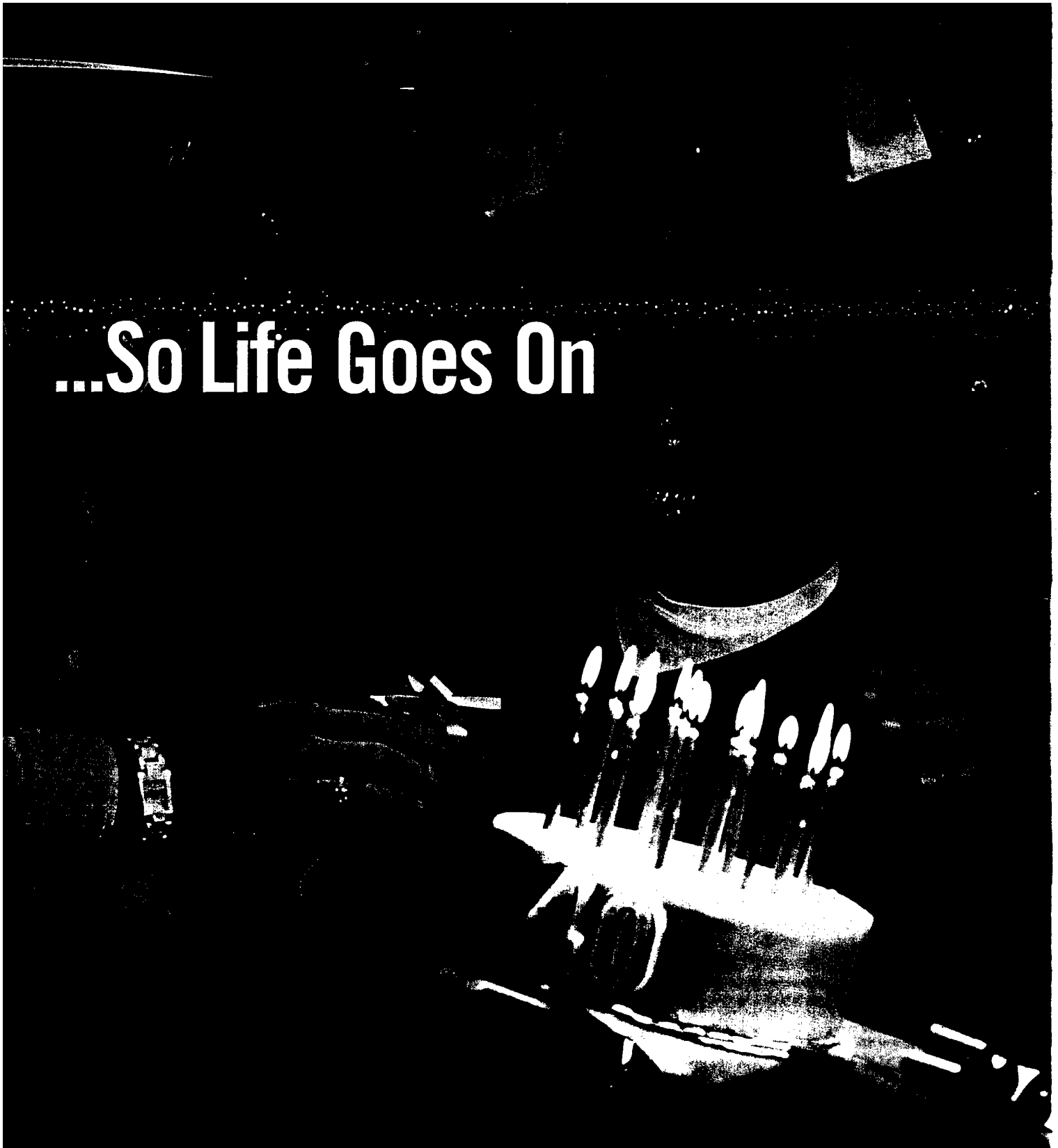
SUSTIVA is generally well tolerated, with fewer gastrointestinal (GI) side effects, such as nausea, vomiting, and diarrhea, than Viracept®*[3]. Diabetes, kidney stones, and life-threatening liver problems are rare.

SAFETY INFORMATION

Many patients have dizziness, trouble sleeping, drowsiness, trouble concentrating, and/or unusual dreams a few hours after starting SUSTIVA. They tend to go away after you have taken the medicine for a few weeks. A small number of patients have had severe depression, strange thoughts, or angry behavior. If you have these symptoms, you should contact your doctor immediately to discuss your therapy. There have been a few reports of suicide, but SUSTIVA has not been established as the cause. Women should not become pregnant while taking SUSTIVA because birth defects have been seen in cynomolgus monkeys given SUSTIVA. See Patient Information about SUSTIVA on the following pages.

Consumer Ad

Once Daily
SUSTIVA™
efavirenz



References: 1. DPC Study 006, Sustiva/ZDV/3TC versus IDV/ZDV/3TC; ACTG 364, Sustiva/NRTIs versus NFV/NRTIs.
2. DPC Study 006, Sustiva/ZDV/3TC versus IDV/ZDV/3TC. 3. ACTG 364, SUSTIVA/NRTIs versus NFV/NRTIs.
*Viracept is a registered trademark of Agouron Pharmaceuticals, Inc.
For further information visit our website at www.sustiva.com or call 1-800-4-PHARMA (1-800-474-2762).
SUSTIVA™ and the SUNBURST LOGO are trademarks of DuPont Pharmaceuticals Company.

DUPONT

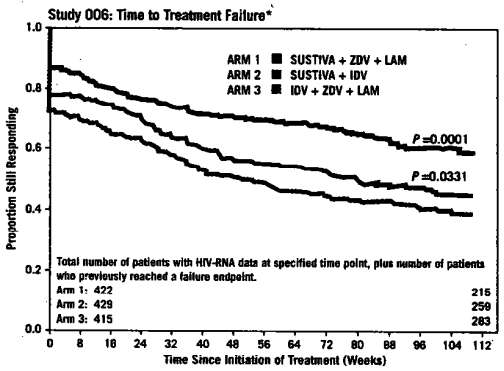
DuPont Pharmaceuticals Company

Printed in U.S.A.

In HIV Combination Therapy

Extending the Limits of Power and Tolerability

NEW > 2-YEAR DURABILITY DATA



*Subjects were considered to have reached the study endpoint at the first time they either experienced virologic rebound (2 HIV-RNA ≥400 copies), had an AIDS-defining event, or discontinued study medication. Those who did not respond to initial treatment were considered to have reached this endpoint at time zero.

PROVEN POWER

- Sustained viral load suppression to <50 copies/mL in patients with high baseline viral loads.[1]
- Superior to protease inhibitor–containing regimens for naive or NRTI-experienced patients.[2]
- Pharmacologic properties may minimize resistance.
  - 40-55 hour half-life with trough levels 26-fold > IC_{90} for wild type isolates.[1]
  - Penetrates the CSF and lymph nodes.[3]
- Only NNRTI listed as part of a "strongly recommended" regimen for initial treatment in DHHS Guidelines.[4]

LONG-TERM TOLERABILITY

- Convenient once-daily dosing, taken with or without food or liquids.
- Generally well tolerated, no long-term toxicities observed.

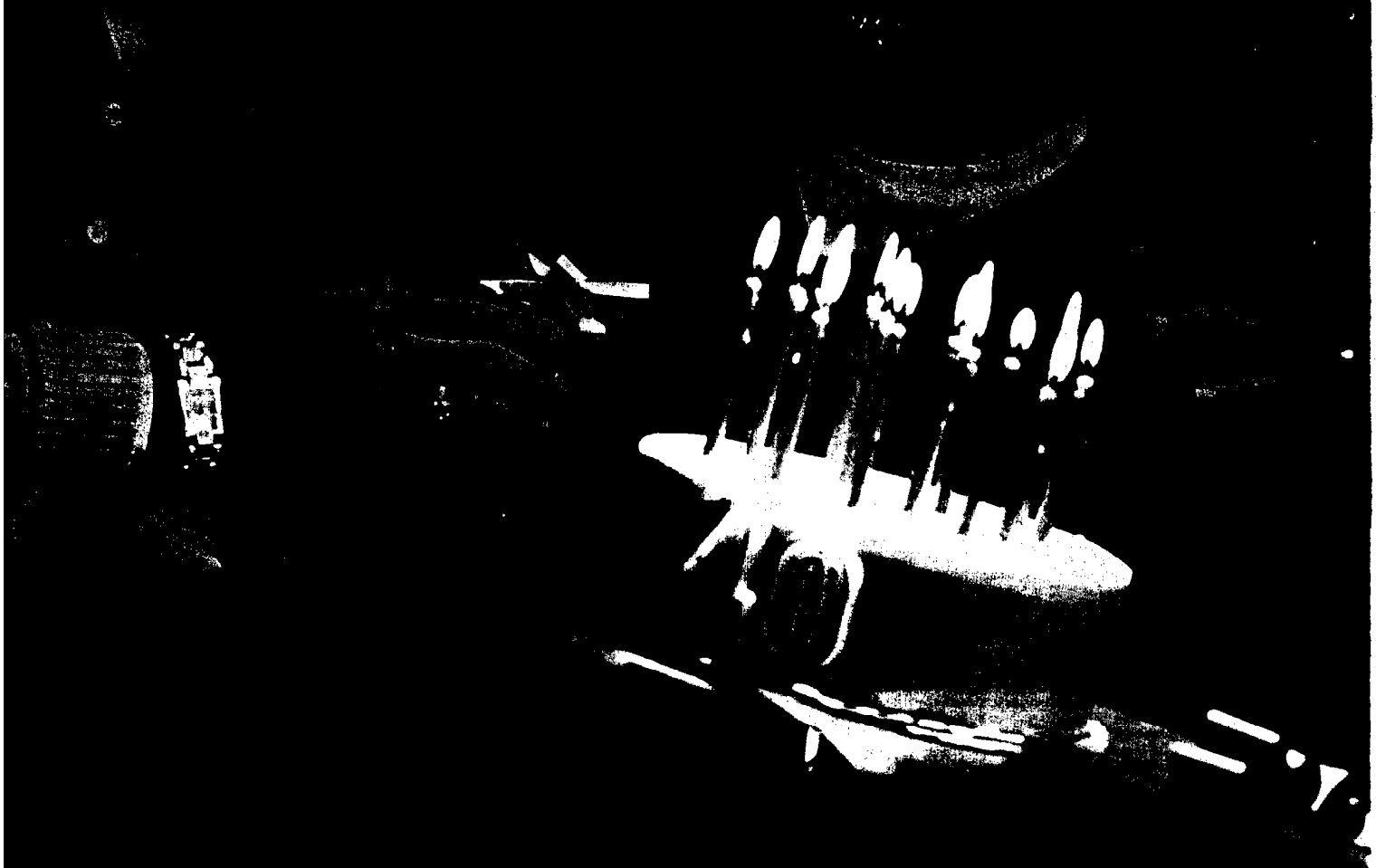
SAFETY INFORMATION

- 53% of patients experienced nervous system symptoms. Generally mild to moderate, they usually begin during days 1 to 2 and resolve after 2 to 4 weeks.
- Serious psychiatric experiences occur in a small number of patients (<1% for specific events). Patients who experience these symptoms should contact their physicians. Nervous system symptoms are not predictive of these less frequent psychiatric symptoms.
- Women should not become pregnant while taking SUSTIVA, because birth defects have been seen in cynomolgus monkeys given SUSTIVA.

Professional Ad

Once Daily
SUSTIVA™
efavirenz

...So Life Goes On



References: 1. Data on file, DuPont Pharmaceuticals Company, Wilmington, DE. DPC Study 006, SUSTIVA/ZDV/3TC versus IDV/ZDV/3TC. ACTG 364, SUSTIVA/nucleoside analogues versus NFV/nucleoside analogues. 2. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med.* 1999;341:1865-1872. 3. Dybul M, Chun TW, Ward DJ, et al. Evaluations of lymph node viral burden in HIV-infected individuals receiving an efavirenz-based protease inhibitor sparing HAART regimen. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, 1999; San Francisco, Calif. Abstract LB-15. 4. *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents.* Panel on Clinical Practices for Treatment of HIV Infection, Dept of Health and Human Services. January 2000:11.

DUPONT®

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Printed in U.S.A.

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