DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

**TRANSMITTED VIA FACSIMILE** JUN 27 2000

Kevin Dransfield
Manager, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

**RE: NDA 20-636 / 20-933**
**Viramune (nevirapine) Tablets and Oral Suspension**
**MACMIS ID #9064**

Dear Mr. Dransfield:

This letter is to inform the Regulatory Affairs Department of Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) that the current web site for Viramune is 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 web site on June 23, 2000. The web site is violative for the reasons cited below.

**Use of Outdated Product Labeling**

The Viramune web site violates the Act because an outdated version of the approved product labeling (PI) is linked to the promotional messages on your www.viramune.com web site. The failure of providing the current PI results in the omission of important safety information as described below.

The Food and Drug Administration (FDA) approved revisions to the Viramune PI in October 1999. These revisions included adding risk information to the boxed warning and other sections of the PI regarding potentially fatal hypersensitivity reactions, as well as adding new drug interaction information. Although the main web page states that the Viramune web site was updated on April 13, 2000, the "Product Information" is linked to

a September 10, 1998 version of the PI. The September 1998 version of the PI fails to include, among other things, information about fatal hypersensitivity reactions that have occurred in patients treated with Viramune, characteristics of these reactions and that Viramune must be discontinued as soon as possible if hypersensitivity is suspected. Your failure to provide the most current PI misbrands Viramune. DDMAC is especially concerned with this violation since the omission of complete information about this potentially fatal adverse reaction associated with Viramune raises significant safety concerns.

**"Product Information" Web Page**

Although DDMAC did not object to a detail aid that contains the same or similar claims as those presented on the Viramune "Product Information" web page, the review was done in 1996 and based on the original PI. Since that review in 1996, the Viramune PI has been revised a number of times, several antiviral agents for HIV have been approved by FDA and the issues surrounding the care of patients with HIV have evolved. Despite the changes cited above, the information on the Viramune "Product Information" web page has not been revised. Important risk information from the current PI is not included on this web page and numerous claims on this web page are misleading.

***Omission of Important Risk Information***

The risk information listed under the heading "Generally well tolerated" is misleading because the information is not complete and the selective presentation of data suggests Viramune is safer than clinical evidence demonstrates. Information regarding the potentially fatal hypersensitivity reaction is not listed. In addition, the risk for potentially fatal hepatotoxicity is minimized by the statement "Because hepatitis has occasionally been reported, liver function tests should be monitored." Finally, adverse reaction data from Trial BI 1046 are not included. The data from this trial are included in the current PI and reflect a higher incidence rate for adverse reactions than currently presented in the table on the web page.

***Misleading Claims***

The claim of "no clinically significant drug interactions" with Viramune is misleading because it minimizes the risk of potentially significant drug interactions. Currently, information in the *Precautions/Drug Interactions* section states that:

- Rifampin/rifabutin should only be used concomitantly with Viramune if clearly indicated and with careful monitoring.
- Oral contraceptives should not be administered concomitantly with Viramune.
- Viramune and ketoconazole should not be administered concomitantly.

- Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Your claim of "no significant drug interactions" is misleading because it implies that Viramune is not associated with drug interactions and it fails to describe important information about the concomitant use of specific drugs with Viramune.

The claim that Viramune possesses "Unique features for patient compliance" is misleading because the features touted as unique to Viramune are no longer unique. For example, Viramune's dosing interval is not unique. A number of antiretroviral drugs, including a non-nucleoside reverse transcriptase inhibitor (NNRTI) like Viramune, are approved for once daily or twice daily dosing. Although more than one tablet or capsule may be required, there is a lack of evidence documenting that patients taking fewer pills at the same dosing interval are more compliant. Thus, these dosing characteristics are inadequate to support your patient compliance claim.

**Patient Information Web Page**

The information found on the "Patient Information" web page contains the same or similar claims from a patient brochure reviewed by DDMAC in 1996. Revisions to the Viramune PI and changes in the standard of care for patients with HIV render much of the information on the web page misleading. The web page contains several statements that imply that monotherapy is an option for patients with HIV. For example, statements such as "Combination class therapy may be more effective against HIV" (emphasis added) are misleading. The current standard of care for patients with HIV is combination therapy. In addition, important risk information is not included in the section titled "Potential Side Effects Associated With Viramune (nevirapine)." For example, information regarding hepatotoxicity and hypersensitivity reactions, both potentially life-threatening adverse reactions, is not included. The combination of out-of-date information regarding HIV therapy and the omission of important risk information poses a significant safety risk to patients accessing the Viramune "Patient Information" web page for information on HIV therapy and Viramune.

BIPI should immediately cease using the Viramune web pages and all other promotional materials for Viramune that fail to provide the current PI or that contain the same or similar claims or presentations. BIPI should submit a written response to DDMAC on or before July 12, 2000 describing its intent and plans to comply with the above. Your response should list similarly violative materials that were discontinued and the discontinuation date.

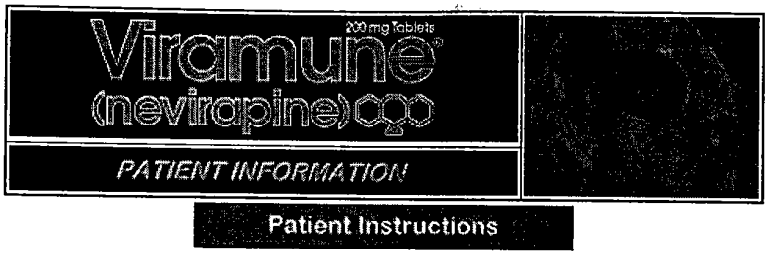
The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your web site and may determine that additional remedial measures will be necessary.

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, Room 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID #9064 and the NDA number. DDMAC reminds BIPI that only written communications are considered official.

Sincerely,

/S/

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






## A NEW CLASS OF HIV THERAPY

Viramune® (nevirapine) is the first in a new class of drugs that treat HIV-1 (human immunodeficiency virus).

Before Viramune®, only two classes of anti-HIV drugs were available: "nucleoside analogues," which includes drugs such as Retrovir® (zidovudine or ZDV or AZT), Zerit™ (stavudine or d4T), Epivir™ (lamivudine or 3TC), Videx® (didanosine or ddI), and Hivid® (zalcitabine or ddC). The other class is called "protease inhibitors" and includes Invirase™ (saquinavir mesylate), Crixivan® (indinavir), and Norvir™ (ritonavir).

Each class of drugs attacks HIV in a different way. Combining drugs from different classes is called "combination class therapy." Studies have shown that drugs for HIV are usually more effective when given in combination than when administered alone. At the present time, Viramune® is indicated for use only in combination with nucleoside analogues. The use of Viramune® in combination with protease inhibitors is not recommended until clinical data are available.

This is an introduction to Viramune® therapy. It does not contain everything there is to know. **If you have any questions about Viramune®, ask your doctor or pharmacist.**

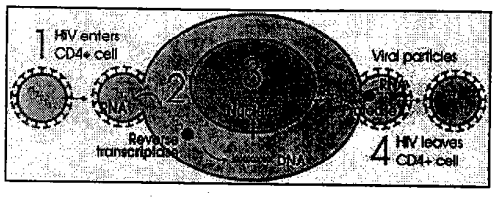
## UNDERSTANDING HIV/AIDS

There are many types of diseases caused by viruses. Some are mild, like the common cold; others are more serious and chronic.

Viruses cannot reproduce directly. They must enter another living cell to make new virus. HIV is an unusual type of virus known as a "retrovirus." Unlike most organisms which use double-stranded DNA to store their genetic information, retroviruses use single-stranded RNA.

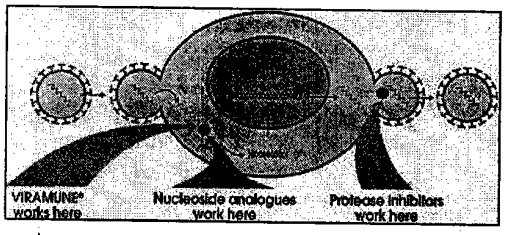
What makes HIV so serious is that it uses the cells of the immune system to reproduce itself. Once HIV enters the body, it targets a type of white blood cell known as a CD4+ cell (or T cell). Once inside the cell, HIV "instructs" the CD4+ cell to make copies of itself. Each infected cell can produce many new viruses, which in a short time may reach into the billions. As HIV infection gets worse, the number of CD4+ cells drops and the weakened immune system slowly loses its ability to prevent disease.

**HIV reproduction in CD4+ cell**




How HIV reproduces: (1) HIV enters a CD4+ cell. (2) The virus uses an enzyme known as reverse transcriptase to turn its single-stranded RNA into DNA (which has two strands). (3) HIV DNA enters the nucleus of the CD4+ cell and inserts itself into the cell's DNA. HIV DNA then instructs the cell to make many copies of the original virus. (4) New virus particles are assembled and leave the CD4+ cell, ready to infect other CD4+ cells.

**How Viramune® (nevirapine) attacks HIV**




Viramune® blocks the reproduction of HIV in a different way than nucleoside analogues or protease inhibitors. By binding tightly to reverse transcriptase, Viramune® prevents viral RNA from being converted into DNA. In contrast, nucleoside analogues are incorporated into the viral DNA and make it ineffective. Protease inhibitors prevent copies of the HIV virus from being successfully assembled and released from the infected CD4+ cell.

## COMBINATION CLASS THERAPY: A MULTIPLE ATTACK ON HIV

"Combination class therapy" is a strategy many doctors are now using to treat HIV disease. It consists of combining drugs from different classes. Adding Viramune® to a treatment regimen of one or more nucleoside analogues is an example of combination class therapy.

Combination class therapy may be more effective against HIV. In a large number of clinical studies, therapy using drugs from different classes has been shown to be better than therapy consisting of just one drug or one class of drug.

Combination class therapy may help reduce the problem of "drug resistance." One of the problems in treating HIV is that the virus can mutate and become resistant to the drugs you are taking. Using a combination of drugs that work in different ways may prolong the time before resistance develops. In addition, even if HIV develops resistance to one drug, the virus may still be affected by the other drug or drugs you are taking.

Because resistance develops rapidly when Viramune® is given alone, it should always be administered in combination with at least one other anti-HIV drug.

## THE MANY BENEFITS OF Viramune® (nevirapine)

- Viramune® in combination with nucleoside analogues has been shown to reduce the amount of virus circulating in the body and to increase CD4+ cell counts.
- Viramune® travels to all parts of the body, including areas that some other antiretrovirals may not reach.

- Viramune® has no known clinically significant interactions with the following antiretroviral drugs: Zidovudine (ZDV), didanosine (ddI), or zalcitabine (ddC). However, Viramune® may interact with other commonly used drugs. Be sure your doctor and pharmacist are aware of all the drugs you are currently taking. They can advise you about any possible interactions with Viramune®.

## POTENTIAL SIDE EFFECTS ASSOCIATED WITH Viramune® (nevirapine)

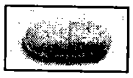
- Viramune® does not cause the types of serious side effects normally associated with nucleoside analogues.
- The most common potential side effects of Viramune® therapy are rash, fever, fatigue, nausea, and headache.
- **The major side effect of Viramune® is rash. Notify your doctor promptly if you develop any rash. Most rashes with Viramune® occur within the first 6 weeks. If you develop a severe rash or a rash accompanied by fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise, stop taking Viramune® immediately and notify a doctor.**
- Most rashes associated with Viramune® therapy are mild to moderate and can be controlled by following the recommendations of your doctor.

## POINTS TO REMEMBER

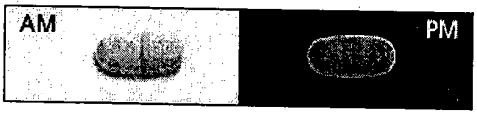
- Viramune® is not a cure for HIV infection. You may continue to experience illnesses associated with HIV infection, including opportunistic infections. Viramune® has not been shown to reduce the incidence or frequency of such illnesses. Therefore, you should remain under a doctor's care while you are taking Viramune®.
- The long-term effects of Viramune® are not yet known.
- Viramune® has not been shown to reduce the risk of transmitting HIV to other people through sexual contact or blood contamination.
- Viramune® may reduce the effectiveness of oral contraceptives and other hormonal methods of birth control. Therefore, you should not use these methods for birth control when taking Viramune®.
- Viramune® may interact with some drugs. Therefore, tell your doctor of any other medications you are taking.

## Viramune® (nevirapine) IS EASY TO TAKE

- Starting dose: Take one 200 mg tablet once a day for the first 14 days. This lead-in period has been shown to reduce the frequency of rash. Inform your doctor if you experience any sort of rash or other side effect.



- Maintenance dose: After the first 14 days, take one 200 mg tablet twice a day thereafter, or as instructed by your doctor. Viramune® tablets should be taken at 12-hour intervals, for example, at 7 am and 7 pm - whatever is most convenient for you. **Do not increase your dose if you experience rash during the "starting dose" period, until the rash has cleared up.**



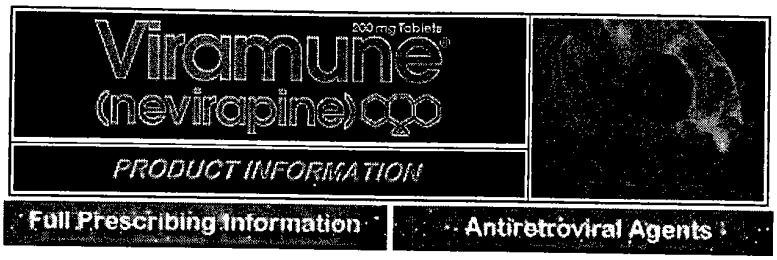

- Take Viramune® every day as prescribed. Do not alter dose without consulting your doctor. If a

dose is skipped, take the next dose as soon as possible; do not double the next dose.
- You can take Viramune® with or without food.
- Store Viramune® tablets at room temperature (59° F to 86° F). Keep bottles tightly closed.



Boehringer Ingelheim
Roxane Laboratories

Introducing a new class of antiretrovirals:
the first non-nucleoside reverse transcriptase inhibitor



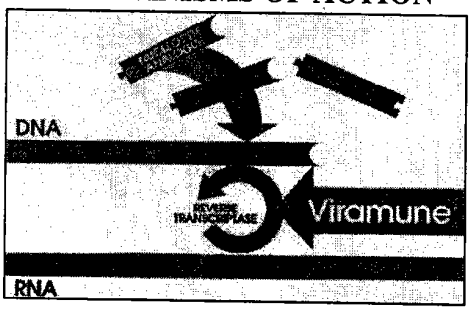

# EXPAND THE ATTACK ON HIV

- Unique mechanism of action
- Unique pharmacokinetic profile
- Uniquely suited for combination class therapy
- Increased effectiveness in combination therapy:
  - nucleoside-experienced patients (ACTG 241)
  - treatment-naive patients (BI 1046)
- Indication
- Generally well tolerated
- Unique features for patient compliance

## Unique mechanism of action

- Binds directly to reverse transcriptase to inhibit production of viral DNA
- Acts at a different site than nucleoside analogues

**MECHANISMS OF ACTION**




Schematic representing activity of nucleoside and non-nucleoside reverse transcriptase inhibitors. Nucleoside analogues are incorporated into viral DNA and block further synthesis. Viramune® acts directly on reverse transcriptase by binding near the enzyme's catalytic site and inhibiting its activity.

## Unique pharmacokinetic profile

- Widely distributed to all tissues; readily crosses blood-brain barrier (n=6) and placenta
- Over 90% bioavailable after oral dosing

## Uniquely suited for combination class therapy

- Synergy shown *in vitro* * with nucleoside analogues†

- No cross-resistance shown *in vitro* * with nucleoside analogues
  - Viramune® remains active against viruses resistant to nucleoside analogues
  - Viramune®-resistant HIV strains remain fully susceptible to nucleoside analogues
- Although early resistance is seen in monotherapy, sustained effectiveness has been shown in combination therapy
- No clinically significant drug interactions which require dosage modification of Viramune® seen with ZDV, ddI, or ddC Viramune® induces hepatic metabolizing enzymes (CYP3A). Dose adjustments may be necessary if co-administered with drugs metabolized by CYP3A

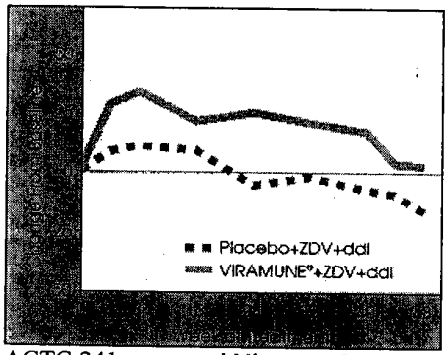
*The relationship between the *in vitro* susceptibility of HIV to Viramune® and the inhibition of HIV in humans has not been established.

†Antiretrovirals studied included zidovudine (ZDV), didanosine (ddI), stavudine (d4T), and lamivudine (3TC).

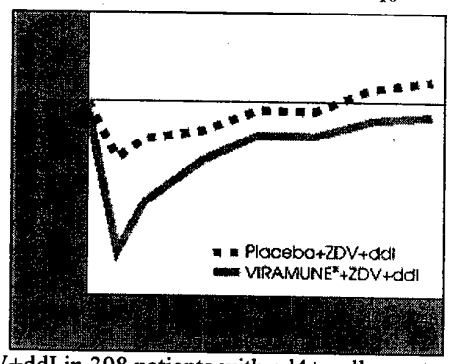
## Increased effectiveness in combination therapy: nucleoside-experienced patients (ACTG 241)

- Sustained improvements in CD4+ cell counts and HIV RNA levels throughout 48 weeks (ACTG 241 study of 398 nucleoside-experienced patients ≥6 months prior nucleoside therapy)

**MEAN ABSOLUTE CELL CHANGE FROM BASELINE (MEAN 153 CELLS/MM³) IN CD4+ CELL COUNTS**



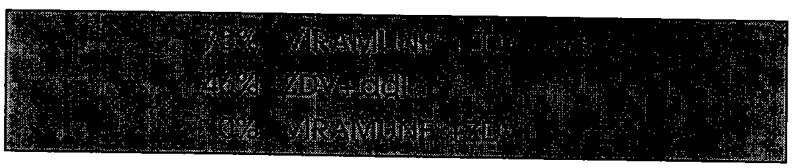

**MEAN CHANGE FROM BASELINE IN HIV RNA CONCENTRATIONS ($LOG_{10}$ COPIES/ML)**




ACTG 241 compared Viramune®+ZDV+ddI vs placebo+ZDV+ddI in 398 patients with cd4+ cell counts at or below 350 cells/mm³ (mean 153 cells/mm³) and a mean baseline plasma HIV RNA concentration of 38,905 copies/mL who had received at least 6 months of nucleoside therapy prior to enrollment (median >2 years). Treatment doses were Viramune® 200 mg/day for 2 weeks, followed by 200 mg b.i.d., or matching placebo; ZDV, 200 mg t.i.d.; ddI, 200 mg b.i.d. HIV RNA concentrations were obtained from a subgroup of 198 patients. The clinical significance of changes in viral RNA with Viramune® therapy has not been established.

## Increased effectiveness in combination therapy: treatment-naive patients (BI 1046)

- 151 patients receiving Viramune®+ZDV+ddI or ZDV+ddI or Viramune®+ZDV
- After 24 weeks, significantly more patients on Viramune® triple therapy had HIV RNA levels below the limit of detection (400 copies/mL)



This study (BI 1046) compared Viramune®+ZDV+ddI vs placebo+ZDV+ddI vs Viramune®+ZDV in 151 patients with CD4+ cell counts between 200 and 600 cells/mm3 (mean 376 cells/mm3) and a mean baseline plasma HIV RNA concentration of 25,704 copies/mL who had received no prior antiretroviral therapy. Treatment doses were

Viramune® 200 mg/day for 2 weeks followed by 200 mg b.i.d. or matching placebo; ZDV, 200 mg t.i.d.; ddI, 125 or 200 mg b.i.d. The clinical significance of changes in viral RNA with Viramune® therapy has not been established.

- After 24 weeks, mean levels of CD4+ cell counts in patients on Viramune®+ZDV+ddI and ZDV+ddI remained significantly above baseline; there was no significant difference between these arms.

## Indication

For use in combination with nucleoside analogues for the treatment of HIV-1 infected adults who have experienced clinical and/or immunologic deterioration. This indication is based on analysis of changes in surrogate endpoints in studies of up to 48 weeks duration. At present, there are no results from controlled clinical trials evaluating the effect of Viramune® with nucleoside analogues on the clinical progression of HIV-1 infection, such as the incidence of opportunistic infections or survival.

## Generally well tolerated

- Does not cause adverse effects primarily associated with other antiretroviral classes, eg, blood dyscrasias, pancreatitis, and neuropathy
- Most frequently reported adverse events related to Viramune® therapy: rash, fever, nausea, and headache

| | Trial BI 1037 & BI 1011 | | ACTG 241* | |
|---|---|---|---|---|
| | All severities | | Grade 3/4 events | |
| | Viramune® +ZDV | ZDV alone | Viramune® +ZDV+ddI | ZDV+ddI |
| Number of patients | 55 | 30 | 197 | 201 |
| Incidence of adverse events (%) | | | | |
| Rash | 20% | 3% | 8% | 2% |
| Fever | 11 | 3 | 3 | 3 |
| Nausea | 9 | 3 | 5 | 4 |
| Headache | 11 | 0 | 3 | 3 |

- Because hepatitis has occasionally been reported, liver function tests should be monitored
- Rash attributable to Viramune® occurred in 17% of patients in combination regimens. Only 7% of patients discontinued therapy due to rash
- **Severe or life-threatening rashes occurred in 7.6% of Viramune®-treated patients compared with 1.2% of patients treated in the control groups. Stevens-Johnson syndrome is an uncommon complication of Viramune® therapy, occurring in 0.5% of patients. Viramune® must be discontinued in patients developing a severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise**
- Rash is usually mild to moderate and resolves without sequelae
- The risk of developing a rash is greatest in first 42 days of therapy
- The recommended 2-week, 200 mg/day lead-in has been shown to significantly reduce the incidence of rash

## Unique features for patient compliance

Simple starting dose:
one 200 mg tablet once daily for 2 weeks. This lead-in period should be used because it has been found to lessen the frequency of rash

Simple maintenance dose:
one 200 mg tablet taken twice daily 

- No dietary restrictions; can be taken with or without food
- May be taken with antacids or ddI (which has an alkaline buffering agent)

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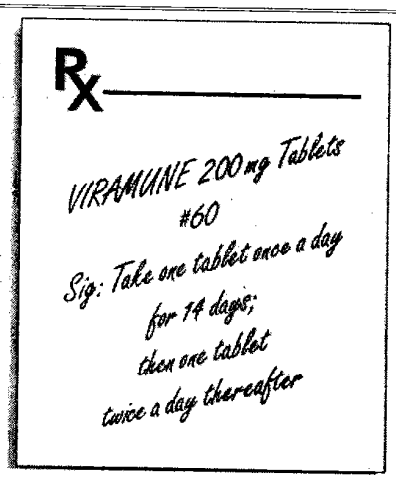
FULL PRESCRIBING INFORMATION






Boehringer Ingelheim
Roxane Laboratories