DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Kevin Dransfield
Senior Associate Director, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

RE: NDA # 20-636, 20-933
Viramune® (nevirapine) Tablets
Viramune® (nevirapine) Oral Suspension
MACMIS ID #12717

Dear Mr. Dransfield:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a direct-to-consumer (DTC) print advertisement (ad) (VR-8515CR) for Viramune® (nevirapine) Tablets and Oral Suspension, submitted by Boehringer Ingelheim Pharmaceuticals, Inc. (Boehringer) under cover of Form 2253. This print ad fails to reveal material facts about Viramune. Specifically, the main part of the print ad fails to disclose limitations on the indication for Viramune, and minimizes the risks associated with Viramune, which can be serious or even fatal. See 21 U.S.C. § 352(n); 21 CFR 202.1(e)(3), (e)(7)(viii). It is important that patients currently taking or considering treatment with Viramune clearly understand these limitations and risks for their own safety.

Background

According to the approved product labeling (PI), Viramune is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Viramune is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. The PI includes the following boxed warning:

> Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in patients treated with VIRAMUNE®. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Women, and patients with higher CD4 counts, are at increased risk of these hepatic events. Women with CD4 counts >250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk of these events. Patients with signs or symptoms of hepatitis must discontinue VIRAMUNE and seek medical evaluation immediately. (See WARNINGS)

> Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE and seek medical evaluation immediately. (See WARNINGS)
>
> It is essential that patients be monitored intensively during the first 18 weeks of therapy with VIRAMUNE to detect potentially life-threatening hepatotoxicity or skin reactions. The greatest risk of severe rash or hepatic events (often associated with rash) occurs in the first 6 weeks of therapy. However, the risk of any hepatic event, with or without rash, continues past this period and monitoring should continue at frequent intervals. In some cases, hepatic injury has progressed despite discontinuation of treatment. VIRAMUNE should not be restarted following severe hepatic, skin or hypersensitivity reactions. In addition, the 14-day lead-in period with VIRAMUNE 200 mg daily dosing must be strictly followed. (See WARNINGS)

The PI also includes, under "Information for Patients," the following additional statements:

> Patients should be informed that VIRAMUNE therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination...
>
> VIRAMUNE is not a cure for HIV-1 infection...

Brief Summary Requirement Violation

The main part of the print ad contains various safety and effectiveness claims for Viramune. The headline "i am taking on tomorrow" [lowercase in original] is followed by "The power to suppress viral load," "Generally well-tolerated," "Twice-daily dosing," and "No food restrictions." Below these claims, there is a paragraph, titled "Important Safety Information for VIRAMUNE," that presents some risk information and contains a small-type reference to the "Patient Product Information" on the adjacent page. This paragraph fails to state that Viramune:

- does not cure HIV;
- does not prevent the transmission of HIV; and
- must be taken in combination with other drugs for HIV infection.

Although these statements are in small print on the adjacent page, they are omitted from the main part of the print ad. 21 CFR 202.1(e)(3)(i).

Minimization of Risk

The print ad is misleading because it fails to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of Viramune. Specifically, in the main part of the print ad, the risk information is presented at the bottom of the page, in a single-spaced paragraph, in small type size, and with poor contrast. The main part of the print ad presents the risk information in non-bolded type against a pale white background, which is

then superimposed over another image, creating a visually distracting presentation that makes the risk information difficult to discern. 21 CFR 202.1(e)(7)(viii).

Conclusion and Requested Action

The main part of the print ad omits important limitations on the indication for Viramune, and fails to present information on the risks associated with Viramune with sufficient prominence and readability. Accordingly, the print ad violates section 502(n) of the Act, 21 U.S.C. § 352(n), and misbrands Viramune.

DDMAC requests that Boehringer immediately cease the dissemination of promotional materials for Viramune Tablets and Oral Suspension the same as or similar to those described above. Please submit a written response to this letter on or before October 6, 2004, describing your intent to comply with this request, listing all promotional materials for Viramune Tablets or Oral Suspension the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at (410) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS #12717 in addition to the NDA numbers. We remind you that only written communications are considered official.

If you choose to revise your promotional materials, DDMAC is willing to assist you in assuring that your revised materials comply with applicable provisions of the Act by reviewing your revisions before you use them in promotion. There are different ways of revising your materials to address the issues identified in this letter. Boehringer could, for example, address the first issue above by adding the missing information. With respect to the second issue, Boehringer could provide greater emphasis for the risk information through the use of bulleting, increased type size, improved contrast, additional spacing, or other techniques apt to achieve emphasis.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Viramune Tablets and Oral Suspension comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

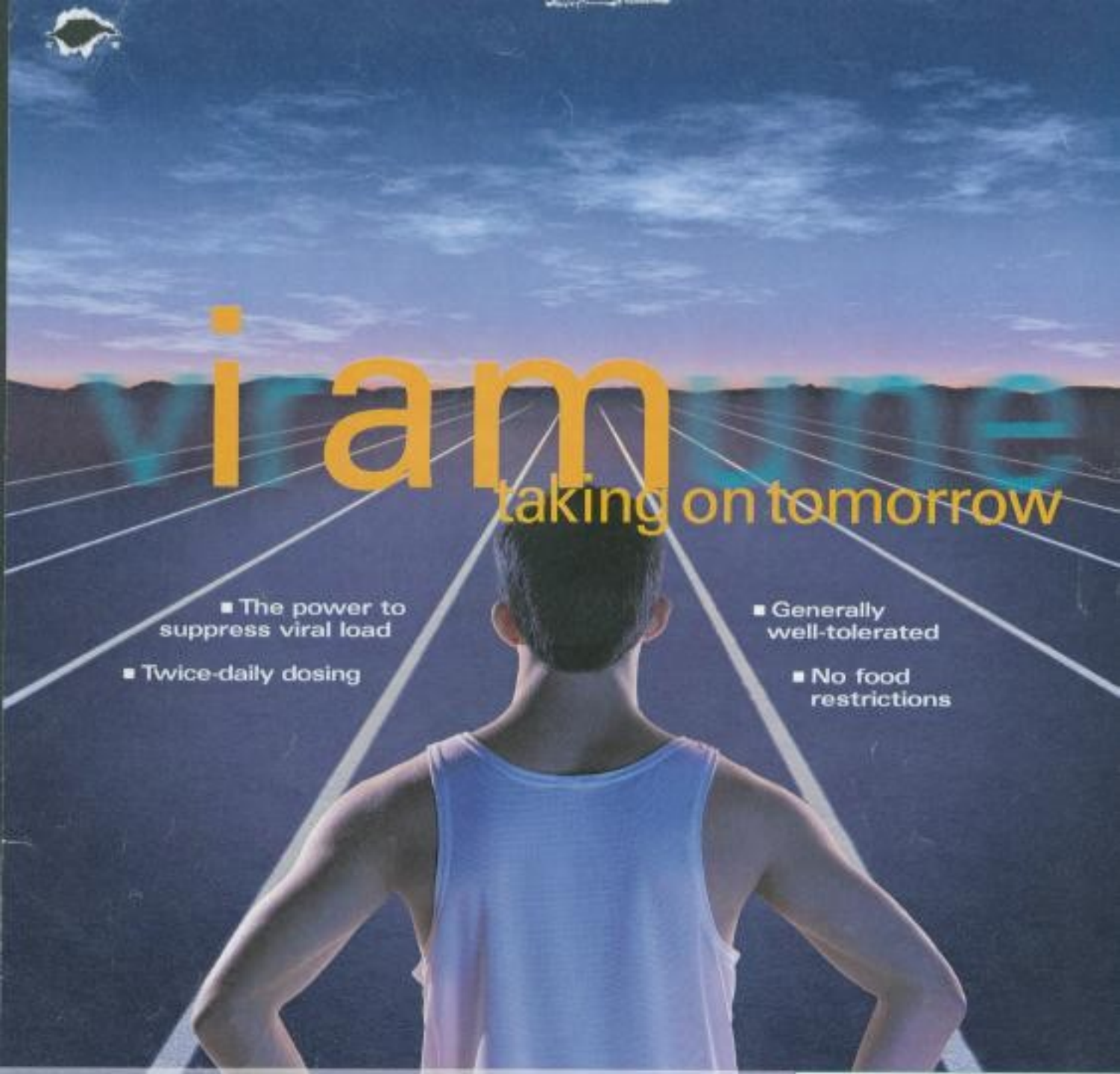
{See appended electronic signature page}

Jennifer C. Murphy, Pharm.D.
Consumer Promotion Analyst
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Jennifer Murphy
9/22/04 10:43:42 AM



VIRAMUNE® (nevirapine) is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Important Safety Information for VIRAMUNE

The most clinically important adverse events associated with VIRAMUNE are rash and hepatic events, including fatal cases of rash. Cases of hypersensitivity reactions have been observed. The greatest risk of severe rash or hepatic events associated with rash occurs in the first 6 weeks of therapy. The first 18 weeks of therapy with VIRAMUNE are a critical period during which it is essential that patients be closely monitored. However, the risk continues past this period and monitoring should continue at frequent intervals. VIRAMUNE should be discontinued and not restarted following severe hepatic, skin or hypersensitivity reactions. Other commonly reported events include nausea and headache. Redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy. The cause and long-term health effects of these conditions are not known at this time. The dose of VIRAMUNE for adults is one 200 mg tablet daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by one 200 mg tablet twice daily.

Please see Patient Product Information on adjacent page.

VR-851CP

tablets, oral suspension
viramune®
nevirapine

Boehringer Ingelheim

www.viramune.com