Boehringer Ingelheim
Roxane Laboratories

IMPORANT DRUG WARNING

Manfred Haehl, MD
Senior Vice President
Medical & Drug Regulatory Affairs

Re: Severe, life-threatening and fatal cases of hepatotoxicity with VIRAMUNE®

Dear Health Care Professional:

Boehringer Ingelheim/Roxane Laboratories, Inc. would like to inform you of important new safety information added to the product labeling for VIRAMUNE® (nevirapine), a non-nucleoside analog indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. The existing labeled warnings for the risk of hepatotoxicity with VIRAMUNE® treatment have been strengthened in response to continued reports of severe, life-threatening and in some cases, fatal hepatotoxicity that have been reported from clinical trials and post-marketing use with VIRAMUNE®.

November 2000

Based on ongoing analyses of clinical trials and post-marketing safety data, Boehringer Ingelheim/Roxane Laboratories, Inc. have further characterized hepatic adverse events associated with VIRAMUNE®. In order to ensure that VIRAMUNE® is used safely and effectively, the Company has revised the product labeling to integrate new clinical data, strengthen warnings, and reinforce the need for careful clinical monitoring of patients during treatment. A copy of the entire revised package insert is attached to this letter; a summary of the most pertinent safety-related revisions is provided below:

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

BOX WARNING , WARNINGS, and ADVERSE REACTIONS:

- The existing sections have been updated to provide additional warning information about the risk of severe, life-threatening and in some cases, fatal hepatotoxicity that have been reported in patients treated with VIRAMUNE®. Although clinical presentation varied among patients, frequently occurring features included non-specific prodromal signs and symptoms of fatigue, malaise, anorexia and nausea, with or without abnormal serum transaminase levels. In these reports, symptoms progressed to jaundice, hepatomegaly, elevation of transaminase levels and hepatic failure over a period of several days. Patients with signs or symptoms of hepatitis must immediately seek medical evaluation, have liver tests performed, and be advised to discontinue VIRAMUNE® as soon as possible.

- **Based on these reports, the first 12 weeks of VIRAMUNE® therapy are a critical period during which intensive clinical and laboratory monitoring, including liver function tests, is essential to detect potentially life-threatening hepatotoxicity and skin reactions.**

- Although most serious hepatic events occurred during the first 12 weeks of VIRAMUNE® therapy, approximately one-third of cases have been reported to occur after this critical period.

- The optimal frequency of monitoring during the first 12 weeks of therapy with VIRAMUNE® has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation and at two weeks post dose escalation. After the initial 12-week period, frequent clinical and laboratory monitoring should continue throughout VIRAMUNE® treatment.

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- Increased AST or ALT levels and/or a history of chronic hepatitis (B or C) infection are associated with a greater risk of hepatic adverse events.
- Serious hepatotoxicity, including liver failure requiring transplantation in one instance, has been reported in HIV-uninfected individuals receiving multiple doses of VIRAMUNE® in the setting of post-exposure prophylaxis, an unapproved use.
- If clinical hepatotoxicity occurs, VIRAMUNE® should be permanently discontinued and not restarted after recovery.

In summary, the need for careful clinical and laboratory monitoring of patients receiving VIRAMUNE® must be emphasized. The diagnosis of hepatotoxicity should be considered for patients presenting with non-specific symptoms of hepatitis even if liver function tests are normal or alternative diagnoses are possible. These considerations are especially critical during the first 12 weeks of therapy, when serious liver toxicity occurs most frequently, but remain important throughout treatment with VIRAMUNE®.

Boehringer Ingelheim/Roxane Laboratories would additionally like to take this opportunity to inform you that the VIRAMUNE® labeling has been modified to provide updated safety information regarding the occurrence of serious skin rashes with VIRAMUNE® therapy. This strengthened information includes a reminder regarding the importance of the 14-day 200 mg lead-in period. It also includes information from a clinical trial in which concomitant prednisone use was associated with an increase in the incidence and severity of rash during the first 6 weeks of VIRAMUNE® therapy. Therefore, use of prednisone to prevent VIRAMUNE®-associated rash is not recommended. Please consult the attached product circular for further information.

Boehringer Ingelheim/Roxane Laboratories has also developed a Patient Package Insert (PPI) that provides patients with the most important information they need to know about VIRAMUNE®. It is intended that the PPI be dispensed with each new prescription and refill, as referred to in the "*Information for Patients*" section of the package insert. A copy of the PPI is attached to this letter for your reference.

You can assist us in monitoring the safety of VIRAMUNE® by reporting adverse reactions to the Boehringer Ingelheim Pharmaceuticals Drug Information Unit at Boehringer Ingelheim Pharmaceuticals, Inc. (800 542-6257, OPTION#4) or to the FDA MedWatch program by telephone at 1-800-332-1088, by FAX at 1-800-332-0178, via www.FDA.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787.

Additional medical information about VIRAMUNE® can be obtained by calling the Drug Information Unit at Boehringer Ingelheim Pharmaceuticals, Inc. (800 542-6257, OPTION#4).

Sincerely,

Manfred Haehl, MD
Senior Vice President
Medical & Drug Regulatory Affairs