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Roxane Laboratories

Roxane Laboratories, Inc.

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VIRAMUNE (nevirapine) / Methadone Interaction

Dear Doctor:

We are writing to inform you of the potential effect that VIRAMUNE® (nevirapine) may have in patients taking chronic methadone maintenance therapy.

Based on the known metabolism of methadone, VIRAMUNE® may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Clinical reports have been received that suggest patients who are taking methadone may experience narcotic withdrawal symptoms when they begin VIRAMUNE® therapy. Therefore, the dose of methadone may need to be increased based on the emergence of withdrawal symptoms in some patients who begin VIRAMUNE® therapy. Methadone-maintained patients beginning VIRAMUNE® therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

VIRAMUNE®, as well as other antiretroviral agents, is a known inducer of cytochrome P450 enzymes including CYP3A4 and CYP2B6. The potential therefore exists to reduce plasma levels of other drugs similarly metabolized, including methadone which is extensively metabolized by cytochrome CYP3A4 in human liver microsomes (Chem Res Toxicology 1996;9:365-73). Post-marketing surveillance by Boehringer Ingelheim Pharmaceuticals, Inc. has identified individuals who have experienced methadone withdrawal symptoms after the initiation of concomitant VIRAMUNE® therapy. Several articles regarding a potential effect of VIRAMUNE® on methadone maintenance therapy have been published. In a preliminary analysis, Staszewski, et al, (Antiviral therapy 1998; 3 [suppl 4]: 55-6) described that 30% of 45 patients

required an increase in their methadone dose thought to be the result of the introduction of VIRAMUNE® therapy. Altice, et al, and Otero, et al, separately reported on patients who experienced opiate withdrawal after the introduction of VIRAMUNE® therapy. Withdrawal symptoms began between 2–15 days after starting VIRAMUNE®. Some patients were maintained on both drugs by upward titration of methadone, but others chose to discontinue VIRAMUNE® (*AIDS* 1999:13:957-62 and 1004-5).

While narcotic withdrawal is a significant concern in HIV-1 infected patients on methadone maintenance therapy, the management of these patients should be balanced with the benefits of antiretroviral therapy. Combinations of antiretroviral agents (highly active antiretroviral therapy [HAART]) are frequently indicated in these patients for control of their HIV infection. Unnecessary discontinuation or modification of HAART can be detrimental to the control of the infection. A number of medications that are indicated for treatment of HIV infection and its complications may contribute to narcotic withdrawal by altering methadone metabolism. In many instances, narcotic withdrawal can be managed successfully in the presence of these drugs, by upward titration of the methadone dose, without discontinuing HAART and jeopardizing otherwise successful control of the HIV infection. We suggest that this approach should be considered for patients who experience narcotic withdrawal symptoms while taking VIRAMUNE®. Methadone-maintained patients beginning VIRAMUNE® therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted according to what is needed to control withdrawal symptoms. These symptoms will generally begin in the first two weeks after introduction of VIRAMUNE®, since most of the metabolic induction caused by nevirapine is realized in the first 14 days of dosing (but may continue through day 28).

If you have any further questions, please call the Roxane Laboratories, Inc./Boehringer Ingelheim Pharmaceuticals, Inc. drug information unit at 1-800-542-6257.

Yours sincerely,

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