IMPORTANT DRUG WARNING INCLUDING BLACK BOX INFORMATION

Dear Healthcare Practitioner:

We have updated the prescribing information for Serzone to warn of rare cases of liver failure leading to transplant and/or death in patients receiving nefazodone HCL. This information is based on postmarketing experience in more than 7.2 million patients in the United States.

The following black box WARNING has been added to the Serzone prescribing information:

Cases of life-threatening hepatic failure have been reported in patients treated with SERZONE.

The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 – 300,000 patient-years of SERZONE treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, 1 patient-year is equal to 2 patients each treated for 6 months, 3 patients each treated for 4 months, etc. (See WARNINGS).

Ordinarily, treatment with SERZONE should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that pre-existing liver disease increases the likelihood of developing liver failure, however baseline abnormalities can complicate patient monitoring.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRECAUTIONS: Information for Patients). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels ³ 3 times the upper limit of NORMAL, while on SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reintroduced. Accordingly, such patients should not be considered for re-treatment.

Additional details of the risk of liver failure associated with Serzone are included in a bolded statement in the WARNINGS section:

> **The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 – 300,000 patient-years of SERZONE treatment. This represents a rate of about 3-4 times the estimated background rate of liver failure. This rate is an underestimate because of under reporting, and the true risk could be**

considerably greater than this. A large cohort study of antidepressant users found no cases of liver failure leading to death or transplant among SERZONE users in about 30,000 patient-years of exposure. The spontaneous report data and the cohort study results provide estimates of the upper and lower limits of the risk of liver failure in nefazodone treated patients, but are not capable of providing a precise risk estimate.

The time to liver injury for the reported liver failure cases resulting in death or transplant generally ranged from 2 weeks to 6 months on SERZONE therapy. Although some reports described dark urine and nonspecific prodromal symptoms (e.g., anorexia, malaise, and gastrointestinal symptoms), other reports did not describe the onset of clear prodromal symptoms prior to the onset of jaundice.

The physician may consider the value of liver function testing. Periodic serum transaminase testing has not been proven to prevent serious injury but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur. Ongoing clinical assessment of patients should govern physician interventions, including diagnostic evaluations and treatment.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRECAUTIONS-Information for Patients). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels $ 3 times the upper limit of normal, while on SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reintroduced. Accordingly, such patients should not be considered for re-treatment.

Because it is difficult to monitor for changes in liver function in patients whose liver function is already abnormal, we have added a statement in CONTRAINDICATIONS:

> SERZONE tablets are contraindicated in patients who were withdrawn from SERZONE because of evidence of liver injury (see Boxed Warning).

In view of the above changes to the SERZONE labeling, the "Information for Patients" section of the PRECAUTIONS has been expanded to warn patients of the potential risk of hepatotoxicity associated with SERZONE therapy:

> *Hepatotoxicity*
> Patients should be informed that SERZONE therapy has been associated with liver abnormalities ranging from asymptomatic reversible serum transaminase increases to cases of liver failure resulting in transplant and/or death. At present, there is no way to predict who is likely to develop liver failure. Ordinarily, patients with active liver disease should not be treated with SERZONE. Patients should be advised to be alert for signs of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

Changes consistent with these WARNINGS have been included in a Patient Package Insert that will be provided with the product packaging. For detailed information on approved indications and additional safety information please refer to the SERZONE package insert. A full copy of the current SERZONE Package insert is enclosed.

Health care professionals are strongly encouraged to report any serious adverse events that occur with the use of SERZONE to 1-800-321-1335 or to the FDA's MedWatch program by phone (1-800-FDA-1088), fax (1-800-FDA-0178), via the MedWatch website at www.fda.gov/medwatch, or by mail (using postage-paid form) to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787.

If you have any questions regarding Serzone tablets please feel free to call Bristol-Myers Squibb at 1-800-321-1335.

Sincerely

Darlene M. Jody, M.D.
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