NDA 20-152/S-028

Bristol-Myers Squibb Company
Attention: Ronald Marcus, M.D.
Group Director, Regulatory Science
Five Research Parkway
Wallingford, CT 06492

Dear Dr. Marcus:

We acknowledge receipt of your supplemental new drug application dated November 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serzone (nefazodone hydrochloride) 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg Tablets.

Supplemental application S-028, submitted under "Changes Being Effected", provides for revisions to Serzone labeling to incorporate the postmarketing data related to Serzone and hepatic failure.

We have completed the review of this supplemental application, S-028, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted November 26, 2001/Label Code1017710B3), which incorporates all of the revisions listed below. Accordingly, this supplemental application is approved effective on the date of this letter.

Specifically, this supplement provides for the following revisions to product labeling.

[Revisions to product labeling.]

SERZONE®
(nefazodone hydrochloride)
TABLETS

Before prescribing SERZONE, the physician should be thoroughly familiar with the details of this prescribing information.

[The addition of a bolded and enclosed black box at the beginning of prescriber labeling.]

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 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.

[Revisions to the **CONTRAINDICATIONS** section.]

CONTRAINDICATIONS

SERZONE tablets are contraindicated in patients who were withdrawn from SERZONE because of evidence of liver injury (see **Boxed Warning**). SERZONE tablets are also contraindicated in patients who have demonstrated hypersensitivity to nefazodone, its ingredients, or other phenylpiperazine antidepressants

[Subsection addition in bolded text to the **WARNINGS** section]

WARNINGS

Hepatotoxicity (See BOXED WARNING)

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. 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 $\geq$ 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.

[Subsection addition to the **PRECAUTIONS-General** section.]

PRECAUTIONS-General
Hepatotoxicity (see **Boxed Warning**)

[Subsection addition to **PRECAUTIONS – Information for Patients** section.]

PRECAUTIONS – Information for Patients:
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.

[Addition of a reference to the WARNINGS section in the ADVERSE REACTIONS-Postintroduction Clinical Experience section.]

ADVERSE REACTIONS-Postintroduction Clinical Experience (2nd paragraph)
Anaphylactic reactions; angioedema; convulsions (including grand mal seizures); galactorrhea; gynecomastia (male); liver necrosis and liver failure, in some cases leading to liver transplantation and/or death (see WARNINGS); …

Labeling changes of the kind which you have proposed under the above supplemental application are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above NDA supplement, have been made.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
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