Bristol-Myers Squibb Company
P.O. Box 4500 Princeton, NJ 08543-4500

June 18, 2004

Dear Healthcare Provider:

We are writing to advise you of some important information regarding SERZONE® (nefazodone hydrochloride) Tablets, an antidepressant approved for the treatment of major depressive disorder in adults. The SERZONE product labeling has been revised to reinforce the importance of doing a thorough risk-benefit analysis when considering prescribing SERZONE for the treatment of depression. In addition, the labeling has been revised to include a warning recommended by the FDA for drugs in the antidepressant class, including SERZONE, concerning the emergence of suicidal ideation and/or attempts in patients taking antidepressants.

Following recent discussions, Bristol-Myers Squibb (BMS) and the U.S. Food and Drug Administration (FDA) agreed to labeling changes for SERZONE that would further encourage healthcare providers to engage in a thorough risk-benefit analysis, including consideration of the risk of hepatic failure associated with SERZONE treatment, when deciding among alternative treatments available for depression. We have revised the **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections of the label as follows.

> **INDICATIONS AND USAGE**
> SERZONE® (nefazodone hydrochloride) is indicated for the treatment of depression. When deciding among the alternative treatments available for this condition, the prescriber should consider the risk of hepatic failure associated with SERZONE treatment (see **WARNINGS**). In many cases, this would lead to the conclusion that other drugs should be tried first.
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> **DOSAGE AND ADMINISTRATION**
> When deciding among the alternative treatments available for depression, the prescriber should consider the risk of hepatic failure associated with SERZONE treatment (see **WARNINGS**).

The FDA has also recently communicated with manufacturers of antidepressants, including BMS, advising of its recommendation that labeling changes are warranted to caution practitioners and patients about the need for close observation of patients being treated with antidepressants for clinical worsening of the symptoms of depression, for the emergence of suicidality, and for the emergence of a variety of other symptoms that may represent a worsening of the patient's condition. The FDA expressly notes that "[a]lthough there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established." In accordance with the FDA, we have ammended our labeling and we want you to be aware of the need to be vigilant for such behaviors.

We have revised the **WARNINGS** section to include the requested changes with respect to the emergence of suicidal ideation as follows:

Clinical Worsening and Suicide Risk

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Prescriptions for SERZONE® (nefazodone hydrochloride) Tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

It should be noted that SERZONE is not approved for use in treating any indications in the pediatric population.

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SERZONE® (nefazodone hydrochloride) Tablets is not approved for use in treating bipolar depression.

Please refer to the enclosed **FULL PRESCRIBING INFORMATION** for a complete discussion of the **INDICATIONS, CONTRAINDICATIONS, WARNINGS** (including **BOXED WARNING** on liver failure), **PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE**.

We hope you find this information helpful. If you have further questions or require additional information, please contact our Medical Communications Department at 1-800-321-1335.

Sincerely,

Freda C. Lewis-Hall, M.D.
Senior Vice President
U.S. Medical Affairs
Bristol-Myers Squibb Company

Enclosure: Package Insert