



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Elizabeth Barbehenn, Ph.D.
Peter Lurie, M.D., M.P.H.
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Public Citizen Health Research Group
1600 20th Street, N.W.
Washington, DC 20009-1001

Re: Docket No. 2003P-0090/CP1 & SUP1

Dear Drs. Barbehenn, Lurie, Stolley, and Wolfe:

This responds to your citizen petition dated March 6, 2003 (Petition), requesting that the Food and Drug Administration (FDA) immediately remove Serzone (nefazodone) from the market because of adverse events associated with the drug. It also responds to the supplement you submitted on October 29, 2003 (Supplement), updating the adverse event data for nefazodone covering the period from April 1, 2002, through May 12, 2003.

For the reasons stated below, your request that we remove nefazodone from the market is denied. We do not agree that the available evidence shows that the drug is unsafe for use under the conditions of use for which it is approved. Accordingly, we conclude that no grounds currently exist to justify withdrawal under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355 (e)). As discussed below, the Agency continues to believe that nefazodone provides a potentially important alternative to other antidepressants and that, although there is a risk of liver injury associated with the drug, the incidence of liver failure appears to be low and is adequately addressed through product labeling. However, we continue to monitor the safety profile of nefazodone and the adequacy of risk management for this drug product.

I. BACKGROUND

The Agency approved Bristol-Myers Squibb's (BMS's) new drug application (NDA) for Serzone on December 22, 1994 (NDA 20-152). Serzone is indicated for the treatment of depression. The first generic nefazodone products were approved on September 16, 2003. There are currently nine approved generic products.

In December 2001, at the request of the Agency, BMS added a black box warning to Serzone's FDA-approved labeling stating that cases of life-threatening hepatic failure had been reported in patients treated with the drug product. The black box warning in Serzone's current labeling reads as follows:

2003P-0090

PDN 1

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. 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.

Generic nefazodone products were required to make conforming changes to include the black box warning in their labeling (*see* section 505(j)(2)(A)(v) of the Act (21 U.S.C. 355 (j)(2)(A)(v)); 21 CFR 314.94(a)(8)(iv)).

Recently, Serzone has been the subject of some international regulatory activity. After discussions with several European regulatory authorities, BMS voluntarily withdrew Serzone from the European market in June 2003. After discussions with Canadian regulatory authorities, BMS announced that it was withdrawing Serzone from the Canadian market in October 2003 and ceased marketing the drug in November 2003. BMS also withdrew Serzone from the market in Turkey in 2003. In May 2004, the company announced that it was withdrawing Serzone from the market in Australia and New Zealand.

On May 19, 2004, BMS announced that for commercial reasons it was discontinuing all sales and manufacture of Serzone in the U.S. market effective June 14, 2004. In the announcement, BMS stated that it decided to discontinue sales of Serzone because generic versions of the drug product are widely available and sales of the branded product have rapidly declined. According to BMS, the manufacturers of generic versions of nefazodone have a combined majority of the U.S. market share. As there are several generic nefazodone products currently approved for marketing in the United States, nefazodone might continue to be marketed in the United States after BMS discontinues its sales of Serzone.

II. DISCUSSION

A. Benefits and Risks of Nefazodone

In your petition and supplement, you request that FDA immediately remove Serzone from the market because it is associated with cases of serious liver toxicity (Petition at 1, Supplement at 1). You conclude that there is no justification to allow Serzone to continue to be marketed because of its poor safety profile and because it offers no advantage in efficacy over the other drugs in its class (Petition at 1 and 5, Supplement at 5). FDA disagrees. As to the specific arguments made in your petition and supplement, as discussed below, the Agency believes: (1) nefazodone may provide an important alternative to other antidepressants; (2) although there is a risk of liver injury associated with nefazodone, the incidence of liver failure appears to be low; (3) available evidence does not indicate how, if at all, nefazodone's metabolism by the liver enzyme CYP3A4 impacts liver toxicity, and the product's existing labeling adequately addresses any risks that might be associated with nefazodone's inhibition of CYP3A4; and (4) the black box warning adequately addresses liver toxicity risk overall (though BMS has recently submitted a labeling change to encourage physicians to consider other treatments).

1. Unique Benefits of Nefazodone

We believe that some patients suffering from depression may benefit from nefazodone in unique ways, and the current labeling allows patients and physicians to decide when the risk-benefit ratio favors use of the product. Depression is a devastating disease that can lead to suicide. Given the seriousness of depression, we believe it is important to have alternative treatments available if possible. The greater the number of effective treatment options available, the more likely it is that a given patient can be successfully treated.

Controlled trials have shown Serzone to be effective as a treatment for patients with major depressive disorder. While studies addressing the comparative effectiveness of nefazodone and other antidepressants have not been performed, considerable clinical experience suggests that a patient who does not respond adequately to a given antidepressant may respond to a different antidepressant. This consideration may be particularly relevant in the case of nefazodone because nefazodone inhibits the reuptake of norepinephrine in addition to inhibiting the reuptake of serotonin, while selective serotonin reuptake inhibitors (SSRIs) used to treat depression only inhibit serotonin reuptake. Because of this differing mode of action, there may be in certain situations a better chance of a patient responding to nefazodone after failing to respond to an SSRI than of responding to another SSRI. The possibility that patients may respond to nefazodone after having failed to respond to another antidepressant provides an important rationale for permitting the continued marketing of nefazodone, given that we believe the risks associated with its use are acceptable in light of the seriousness of depression, as discussed below.

Significantly, nefazodone also does not appear to be associated with the frequent sexual side effects seen with SSRIs. It has been observed in the clinical setting that these side

effects can cause a patient to discontinue treatment prematurely. Nefazodone seems also to be free of side effects that limit the usefulness of other available antidepressants (e.g., weight gain with drug products such as Remeron, serious cardiac events with the tricyclics). Because these side effects can be dangerous and/or intolerable enough to lead to discontinuation of treatment, it is all the more desirable to have other options available to patients, if the toxicities of these options are acceptable. That nefazodone lacks these side effects further supports allowing the drug to remain on the market.

2. *Liver Failure Resulting in Death or Transplant*

In your petition, you state that Serzone was associated with at least 53 cases of liver injury, including 21 cases of liver failure (resulting in 11 deaths) (Petition at 1, 3-4). Data on adverse events discussed in the petition covered the period from December 1994 through March 31, 2002. In the supplement, you update the data to cover the subsequent time period of April 1, 2002, through May 12, 2003. Based on your review of these data, you conclude that during the latter period 41 additional cases of liver toxicity, including 9 deaths and 5 liver transplants, occurred (Supplement at 2). You also state that 2 additional cases of liver toxicity are reported in the literature, but not in the FDA database (Supplement at 3).

Particularly since 1999, FDA has been closely monitoring reported acute liver failure cases associated with nefazodone. While reviewing and evaluating the liver failure reports submitted to us by BMS and submitted directly to FDA's Adverse Event Reporting System (AERS) through June 8, 2004, we found that the rate for liver failure resulting in death or transplant may have declined since 2001. In particular, since the addition of the black box warning in December 2001 through June 8, 2004, the Agency has received a total of 18 reports of liver failure associated with nefazodone. However, while these reports were received after inclusion of the black box warning on the nefazodone labeling, your conclusion is incorrect that they indicate an increased incidence of liver failure occurring after the inclusion of the black box warning. Of the 18 reports, 15 represent events that occurred *prior to the black box labeling changes*. Of the remaining three cases, two occurred after the labeling changes. However, neither of these two cases was well documented. The remaining case did not contain a date for the onset of the liver failure; consequently, we cannot determine whether that event occurred prior to, or after, the adoption of the black box warning.

We believe that the incidence of liver failure leading to death or transplant is low. As stated in the black box warning, the reporting rate corresponds to a rate of one in 250-300,000 patient-years. Spontaneous events are known to be underreported, however. Assuming only 10 percent of events were reported as you suggest (Petition at 2, Supplement at 4), the rate would correspond to one in 25-30,000 patient-years. A large epidemiologic study has helped place an upper bound on this rate, finding no events in about 30,000 patient-years of exposure.¹ This corresponds to an incidence of acute liver failure resulting in death or transplant associated with nefazodone treatment of not more

¹ See "Warnings" section in Product Labeling for Serzone (nefazodone hydrochloride).

than 1/10,000 patient-years. The rate of liver injury resulting in death or transplant in the general population is considered to be about 1 case/1,000,000 patient-years.

Through the review of post-marketing adverse event reports available to us on nefazodone related to liver injuries, we identified and evaluated reports involving serious liver injuries (i.e., those involving liver failure resulting in death or transplant). We did not separately evaluate these post-marketing adverse event reports to assess liver injuries of lesser severity (i.e., adverse events not involving death or liver failure) and do not consider such an evaluation necessary in this instance.² The primary clinical concern related to a drug's capacity to induce less severe liver injury generally is that these lesser changes might be predictive of a drug's potential to cause, in some cases, liver failure. That is, the less severe liver injuries, in and of themselves, typically would not be considered intrinsically dangerous, but would raise concerns that more significant, clinically important damage could occur (e.g., liver failure). We have, however, already concluded that nefazodone is capable of inducing liver failure. A detailed examination of post-marketing adverse event cases of less severe injury would not change this conclusion. We believe that we have, based on the epidemiologic data described earlier, as good an estimate of the maximum rate of nefazodone-induced liver failure as it is possible to have at this time. Further evaluation of cases of less severe liver injury would not alter this estimate or change our view about whether or not nefazodone is capable of causing liver failure.

3. *Liver Toxicity and CYP3A4*

You state that Serzone causes an increased risk of toxicity because it is both metabolized by and inhibits a key enzyme in the liver (CYP3A4) that detoxifies drugs (Petition at 4-5, Supplement at 3-4). You maintain that because of this inhibition, nefazodone can cause increases in plasma levels of other drugs that rely on CYP3A4 (Petition at 4, Supplement at 3). You also state that the nonlinear increase in plasma levels of nefazodone and its metabolites due to nefazodone's metabolism by CYP3A4 adds to the degree of difficulty in prescribing since concentrations of the active drug increase more than proportionately with both dose and time (Petition at 4).

Many drugs currently on the market have similar effects involving CYP3A4. Physicians should be sensitive to these effects and should be aware of all drugs their patients are taking so that they can manage any potential interactions. That a drug inhibits or is metabolized by CYP3A4 in no way poses a bar to the safe use of the drug, however, except under extraordinary circumstances (e.g., if inhibiting CYP3A4 elevated the level of the drug by many multiples and this elevated level was known to be unacceptably toxic).

² Because there are no reliable background rates (the rates of occurrence in the non-drug-treated population) available for less severe liver injury (e.g., elevation of liver enzymes), we would also be unable to systematically evaluate the post-marketing reports of cases of liver injury less severe than those resulting in transplant or death. Without background rates, we cannot determine if the number of cases of less severe toxicities reported in patients being treated with nefazodone reflect an incidence rate above the background rate for these events. Without this comparison, we cannot accurately assess nefazodone's role in their occurrence.

With respect to whether nefazodone is a substrate for (i.e., is metabolized by) CYP3A4, some in vitro studies suggest that CYP3A4 is involved in the metabolism of nefazodone, but we are unaware of any evidence suggesting that this metabolic action occurs in humans. Even if CYP3A4 is an important metabolizing enzyme in humans, we do not know if this is an important fact in relation to the issue of liver toxicity.

We do not know what is responsible for the liver toxicity; it might, for example, be nefazodone itself, one or more of its metabolites, or some combination. We also cannot determine the effects of giving patients another potential inhibitor of CYP3A4. Because nefazodone itself inhibits CYP3A4, adding another CYP3A4 inhibitor might not have much of an effect on nefazodone levels. Further, even if adding another CYP3A4 inhibitor were to markedly increase nefazodone levels, we do not know what the toxicity effects of this increase might be. Such an increase in nefazodone levels would be expected to be accompanied by a decrease in the formation of an important active metabolite because inhibiting CYP3A4 would also limit its availability to metabolize nefazodone. It is possible, therefore, that this collective effect of inhibiting CYP3A4 might increase or decrease liver toxicity; again, we do not know what is responsible for this toxicity. Further, we have no evidence that the liver toxicity, if it is due to nefazodone itself, is worse with increased doses. Consequently, increasing nefazodone levels in and of itself (by inhibiting CYP3A4) might have no effect on the incidence or severity of the liver toxicity. In any event, as explained above, although there is some risk of acute liver toxicity associated with nefazodone treatment, the incidence appears to be low.

As for nefazodone being an inhibitor of CYP3A4, the nefazodone labeling contains warnings, including bolded warnings, and contraindications alerting the prescriber to the interactions that result with particular drugs due to the CYP3A4 inhibition. In addition, language about Serzone as a CYP3A4 inhibitor appears in other sections of the labeling. Furthermore, increasing the plasma levels of other drugs (secondary to CYP3A4 inhibition) would be expected to have no effect on the intrinsic capacity of nefazodone itself to cause liver injury. We believe that the current language in the labeling adequately addresses the potential consequences of nefazodone's capacity to inhibit CYP3A4.

4. *Effectiveness of Black Box Warning*

You state that an increasing number of serious adverse reaction reports relating to liver toxicity associated with the use of Serzone led the Agency to require the addition of a black box warning to the drug's labeling. You argue that labels are often an insufficient substitute for a ban and they are ineffective in preventing drug-induced injuries. You conclude that it would be "extremely unlikely" for letters or label changes to stem the number and severity of the adverse events occurring with Serzone (Petition at 3). Your supplement indicates that liver injury cases continued to be reported following the addition of the black box warning. As discussed above, you conclude that between April 2002 and May 2003, there were 41 cases of liver toxicity associated with the use of

Serzone, including 9 deaths and 5 liver transplants, compared to 11 deaths and 7 transplants in the previous 7 years (December 1994 through March 2002) (Supplement at 2).

However, as discussed above, the event dates from the reports you cite indicate that the great majority of the events reported in this more recent period actually occurred prior to the addition of the black box warning to the Serzone labeling. It is possible that the black box warning stimulated the reporting to FDA of these additional older cases.³ The Agency has not received any reports of well-described cases of acute liver failure resulting in death or transplant occurring since the inclusion of the black box warning. Based on the data available to the Agency, we conclude that there is no evidence indicating an increase in liver failure cases resulting in death or transplant associated with nefazodone (in fact, the data suggest that there might be a decrease in such cases).

Although labeling changes, such as black box warnings, are not always effective in reducing adverse events, we believe that they can be a useful tool in many instances. In the case of nefazodone, we believe that the black box warning has been helpful in allowing physicians and patients to make informed decisions about treatment with the drug product. As mentioned above, the great majority of the reported acute liver failure cases resulting in death or transplant occurred prior to the inclusion of the black box warning in the labeling. In addition, data suggest that the black box warning and the "Dear Health Care Practitioner" letter announcing this labeling change have influenced the prescribing of nefazodone. After the addition of the black box warning, use of Serzone dropped by more than 50 percent. From August 2000 through July 2001, an estimated 4,754,000 prescriptions were written for Serzone. The black box warning was added to the labeling in December 2001. From August 2001 through July 2002, the estimated number of prescriptions dropped to 3,907,000, and from August 2002 through July 2003, Serzone use declined further to 2,270,000 estimated prescriptions. From August 2002 through July 2003, Serzone accounted for approximately 1.3 percent of total dispensed newer antidepressants, down from a high of 3.8 percent in the period of August 1999 through July 2000. As the first generic nefazodone product was not approved until September 2003, none of this decline in Serzone sales can be attributed to generic competition. This decline in prescriptions may, however, be a result of physicians and patients responding to the black box warning and seriously considering the risk before they decide to initiate or continue treatment with nefazodone.

BMS will no longer market Serzone after June 14; however, as noted above, generic nefazodone products might still be available after that date. Although we believe that the safety concerns do not compel the withdrawal of nefazodone from the market under section 505(e) of the Act, the safe use of nefazodone could be improved by enhancing the risk management of this product, such as by adding additional warnings and/or other

³ Spontaneous reporting systems are considered signal generation tools (i.e., they provide an indication of what kinds of events are occurring) and are not considered capable of precise event rate estimates due to potential underreporting. Reporting rates also suffer from the inaccuracy related to the estimates of use. Consequently, although the reported data do not provide affirmative evidence of increased liver failure risk at this time, we recognize that these data cannot be relied upon as providing precise estimates of liver failure. We will continue to monitor reported cases.

changes to the labeling. To that end, BMS has submitted a Changes Being Effected supplement under 21 CFR 314.70(c)(2), which the Agency has approved, to discourage the use of nefazodone as a first-line drug (i.e., to encourage physicians to consider using other treatments first).⁴ Manufacturers of generic drug products are required to make conforming labeling changes under such circumstances.⁵ We will continue to monitor the safety of nefazodone as new information becomes available.

B. Actions Taken in Other Countries

With respect to regulatory actions, you state that other countries have taken stronger actions against Serzone, and you contend that FDA has failed to adequately protect residents of the United States (Petition at 2-3, Supplement at 2-3). You mention that Serzone has been removed from the European market (voluntarily withdrawn by BMS), from the Canadian market in October 2003, and from the market in Turkey (Petition at 2-3, Supplement at 1-2). You state that BMS removed Serzone from the European market because different European regulatory authorities had either adopted or were considering a liver enzyme monitoring requirement to be included in the product's labeling (Petition at 2-3).

Although FDA regularly takes note of the actions of other national or international regulatory authorities, those actions do not control our decision-making. Other countries have different regulatory procedures for reviewing adverse events for drug products and for making risk-benefit evaluations. Nevertheless, FDA regularly monitors foreign regulatory activity regarding the safety of drug products marketed in the United States and makes decisions based on all of the information available to us, including both foreign and domestic data. We are aware that Serzone has been removed from the market in many other countries. As stated above, BMS has recently voluntarily withdrawn the product from the U.S. market as well. We have considered all of the relevant data on nefazodone independently, however, and have concluded that, with appropriate labeling, the benefits of permitting the continued marketing of nefazodone outweigh the risks.

III. CONCLUSION

The data available to the Agency, including data from AERS, BMS, and the review and approval history of Serzone, do not support the removal of nefazodone from the market. For treating depression, the availability of several treatment options, including nefazodone, is important. The decision to allow nefazodone to remain on the market is based on our conclusions that (1) the drug may provide important benefits for patients

⁴ See Approval Letter for NDA 20-152/S-034 (May 27, 2004) (available on the Internet at <http://www.fda.gov/cder/foi/appletter/2004/20152sr034ltr.pdf>).

⁵ Section 505(j)(2)(A)(v) of the Act; 21 CFR 314.94(a)(8)(iv).

Docket No. 2003P-0090/CP1 & SUP1

who have not benefited from or tolerated other available treatments and (2) the risk of liver injury is sufficiently conveyed in the black box warning and other labeling statements. Although we are denying your request that we remove nefazodone from the market, we will continue to monitor the drug's safety to determine whether further risk management steps are appropriate.

Sincerely,

A handwritten signature in black ink, appearing to read 'S. Galson', written in a cursive style.

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research