Public Citizen

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Joan Claybrook, President

March 6, 2003

Mark B. McClellan, M.D., Ph.D., Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20854

Dear Commissioner McClellan:

Public Citizen, representing 125,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately remove from the market Serzone (nefazodone; Bristol-Myers Squibb), a widely prescribed drug for the treatment of depression with over 4.5 million prescriptions a year. Bristol-Myers Squibb has already withdrawn nefazodone from the European market as a consequence of reports of serious liver toxicity (January 8, 2003). Our own analysis, based on adverse reaction reports to the FDA, revealed that, from 1994, when first marketed, through the first quarter of 2002, nefazodone was associated with at least 53 cases of liver injury including 21 cases of liver failure from which 11 people died (see Appendices 1 and 2).

Bristol-Myers Squibb has recently acknowledged a worldwide total of "28 reports of liver failure leading to necrosis or death" (18 of the 28 patients died).[1] Based on 1) the European withdrawal, 2) our own analysis of FDA Adverse Event Reports (AERS), 3) the fact that the drug has no unique therapeutic benefit over many other antidepressants, plus 4) the fact that "periodic serum transaminase testing has not been proven to prevent serious injury" and 5) that "there is no way to predict who is likely to develop liver failure,"[2] there can be no justification for continuing to market this dangerous drug. We petition for the removal of nefazodone from the market in the U.S. as has been done in Europe.

[1] Hawaleshka D. How dangerous is serzone? Maclean's magazine. February 24, 2003. Available at: http://www.macleans.ca/xta-asp/xtaquery.asp. Accessed February 27, 2003.
[2] Serzone label. Available at: http://www.fda.gov/cder/foi/label/2002/20152slr009lbl.pdf Accessed February 13, 2003.

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Reports in the medical literature

Liver toxicity associated with nefazodone has been a concern for more than four years: in 1998, reports from Australia highlighted hepatic dysfunction as being "of particular importance."[3] Included in the Australian report were three cases of jaundice and a liver biopsy in one patient consistent with drug-induced hepatitis.

In early 1999, in the U.S., a group of physicians reported three cases of nefazodone-induced liver failure appearing 3 to 8 months after drug initiation. Liver biopsies revealed a similar "prominent necrosis" in all three. One patient, a 16-year-old, required a liver transplant to survive; another had a liver transplant but died.[4] These cases appear to be included in the AERS database.

In Spain, a group of independent researchers, using the Spanish Pharmacovigilance System database combined with drug sales data obtained from the Spanish National Health System, warned that some antidepressants could cause hepatitis. Of the 13 antidepressants examined, nefazodone had the highest incidence of hepatic injury, 7 to 22 times that of the other antidepressants although the absolute number of cases for most drugs was low.[5]

Stronger Actions Taken in Other Countries

In June 2001, Bristol-Myers Squibb sent a safety advisory to Canadian physicians warning of "very rare reports of severe liver injury temporally associated with the use of nefazodone." A subsequent analysis of adverse event reports from the Canadian Adverse Event Drug Reaction Monitoring Programme found 38 cases of liver injury associated with nefazodone with 31 of these listed as "severe" or "serious." These latter reports included three cases of hepatic failure, one case of hepatic degeneration, one case of necrosis, and one case of fulminant hepatitis.[6] Most developed within 6 months of starting nefazodone, a much longer time frame than the 6-8 weeks exposure of the pivotal clinical trials (a duration inadequate to detect these "delayed" reactions).

Due to continuing reports of liver damage related to nefazodone, the Swedish Medical Products Agency announced a liver enzyme monitoring requirement that was to be included in the product's labeling.[7] Rather than accept this requirement, Bristol-Myers Squibb withdrew the drug from the Swedish market (January 1, 2003). A number of other European countries were considering a

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[3] Australian Adverse Drug Reactions Bulletin, November 1998;17:1.
[4] Aranda-Michel J, Koehler A, Bejarano PA, et al. Nefazodone-induced liver failure: report of three cases. Annals of Internal Medicine 1999;130:285-288.
[5] Garcia-Pondo AC, Garcia del Pozo J, Sanchez Hepatotoxicity associated with the new antidepressants. J Clin Psychiatry 2002;63:135-137.
[6] Stewart DE. Hepatic adverse reactions associated with nefazodone. Canadian Journal of Psychiatry 2002;47:375-377.
[7] Scrip December 11, 2002; No 2806, p.19.

similar monitoring requirement resulting, in January 2003, in Bristol-Myers Squibb withdrawing nefazodone from the entire European market.[8]

While many patients in other countries are now protected from nefazodone-induced injury, the FDA has failed to adequately protect U.S. residents. In January 2002, the increasing numbers of serious adverse reaction reports relating to liver toxicity led the FDA to require the addition of a black box warning and an expansion of the Warnings section of the drug's professional product labeling.[9] The black box warns of "life-threatening hepatic failure . . . in patients treated with SERZONE" and recommends that patients be withdrawn from nefazodone "if clinical signs or symptoms suggest liver failure," including elevations of liver enzyme levels ≥3 times the upper limit of normal.[10]

Unfortunately, labels have often proven to be an insufficient substitute for a ban. Labels are often ineffective in preventing drug-induced injuries, and, in this case, end up presenting a very confused message. Thus, in spite of suggesting the importance of liver function tests in the black box warning, the label also says: "The physician *may consider* the value of liver function testing" [italics added] while adding that no specific laboratory tests are recommended. Elsewhere in the label, it says, "Periodic serum transaminase testing has not been proven to prevent serious injury" and furthermore, "At present, there is no way to predict who is likely to develop liver failure."[11]

The FDA's Drug Risk Assessment Group, along with individuals from medical schools and health care organizations, has analyzed the consequences of post-marketing label changes. Its data clearly showed that black-box warnings and "Dear Health Care Professional" letters had little or no beneficial or preventive effect for troglitazone and cisapride.[12,13] As a result, it seems extremely unlikely that letters or label changes would stem the number and severity of the adverse events occurring with nefazodone, especially when in conflict with aggressive marketing practices.

Adverse Reactions to Nefazodone in FDA's own Database

We searched the AERS database from 1994 through the first quarter of 2002 for liver adverse reactions, looking only for those reports where either nefazodone or

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[8] Scrip January 15, 2003; No 2815, p.21.
[9] Serzone label. Available at: http://www.fda.gov/cder/foi/label/2002/20152slr009lbl.pdf. Accessed February 13, 2003.
[10] Liver enzymes, AST and ALT, are measures of liver toxicity when they escape from the liver into the bloodstream.
[11] Serzone label. Available at: http://www.fda.gov/cder/foi/label/2002/20152slr009lbl.pdf. Accessed February 13, 2003.
[12] Graham DJ, Drinkard CR, Shatin D, et al. Liver enzyme monitoring in patients treated with troglitazone. JAMA 2001;286:831-833.
[13] Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride. JAMA 2000;284:3036-3039.

Serzone was considered the primary suspect. Patients ranged in age from 14 to 87 (Appendices 1 and 2).

Our search revealed 11 deaths; four of the patients that died had had liver transplants. In addition, there were 42 non-fatal hepatic adverse events including 2 cases of hepatic necrosis, 11 cases of hepatic failure, and 3 liver transplants (Appendix 2). Twenty-nine of the non-fatal reactions (71%) required hospitalization. Patients were quite young overall: the median age was 42 years with four patients in their teens (14, 16, 16, and 19). Because of the well-known low rate of spontaneous adverse event reporting, all the numbers in the AERS database can probably be multiplied by 10, at least, as an estimate of the true situation.

Other Dangers of Nefazodone

One of the reasons for the increased toxicity of nefazodone is that it is both metabolized by and inhibits a key enzyme in the liver that detoxifies drugs (cytochrome P450 3A4). CYP3A4 is thought to be involved in the metabolism of about 50% of all the drugs currently prescribed. Thus, any change in the activity of this enzyme is a key predictor of drug responsiveness and toxicity both for nefazodone itself and any drugs administered simultaneously.[14]

Because of CYP3A4 inhibition, nefazodone can cause dramatic increases in plasma levels of other drugs that rely on CYP3A4 for their removal from the body. One example is the 50-fold increase in buspirone (Buspar) drug levels when given with nefazodone to healthy volunteers.[15] There are also warnings in the nefazodone label of many other dangerous drug interactions (a list that is almost certainly not complete): alprazolam (Xanax), triazolam (Halcion), cisapride (Propulsid), pimozide (Orap), fluoxetine (Prozac), haloperidol (Haldol), desipramine (Norpramine), carbamazepine (Tegretol), monoamine oxidase inhibitors, "general anesthetics and other CNS-active drugs," digoxin, HMG-CoA reductase inhibitors (statins), alcohol, and immunosuppressive agents. In addition, by inhibiting its own metabolism, nefazodone can increase its own concentration with potentially toxic results.

The effects of age on toxicity are unknown because there were "too few elderly patients in these trials to reveal possible age-related differences in response."[15]

The non-linear increase in plasma levels of nefazodone and active metabolite adds another degree of difficulty in prescribing since concentrations of active drug increase more than proportionately with both dose and time (Table 1).

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[14] Tirona RG, Lee W, Leake BF, et al. The orphan nuclear receptor HNF4α determines PXR- and CAR-mediated xenobiotic induction of CYP3A4. Nature Medicine 2003;9:220-224.
[15] Serzone label. Available at: http://www.fda.gov/cder/foi/label/2002/20152slr009lbl.pdf. Accessed February 13, 2003.

Table 1. Plasma Drug Levels

Protocol	Expected plasma drug level	Observed plasma drug level
Increase dose from 200 mg to 400 mg	Increase 2-fold	Increased 4-fold
300 mg/day after 5 days compared with 300 mg at day 1	Same as day 1	Increased 5- to 7-fold

CONCLUSIONS:

What is the rationale for allowing nefazodone to remain on the market? It cannot be because of efficacy: a review of the newer pharmacotherapies for depression by the Agency for Health Care Policy and Research concluded that, "In general, there are no significant differences in efficacy between newer antidepressants and first and second generation tricyclic antidepressants nor among different classes of newer antidepressants."[16] More specifically, the review found that, "nefazodone did not differ significantly from older agents" (the examination included the five studies that met their selection criteria, comparing nefazodone efficacy with the older tricyclic antidepressants).

Neither can the rationale for maintaining nefazodone on the market be because of safety. Nefazodone appears to be one of the most dangerous antidepressants marketed: nefazodone-induced liver toxicity cannot be predicted in any individual, there is no way to safely monitor for it, nor is there any way to guarantee that once diagnosed, patients' lives can be saved. While Bristol-Myers Squibb has withdrawn nefazodone from Europe, the U.S. is left with a drug that adds nothing in terms of efficacy while putting patients at risk for life-threatening liver toxicity. Because of its inhibition of and metabolism by the key drug-metabolizing enzyme in the liver, nefazodone has a high propensity for adverse events and drug interactions.

ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

[16] Agency for Health Care Policy and Research. Treatment of depression: newer pharmacotherapies. February 1999. Available at: http://www.ahcpr.gov. Accessed January 30, 2003.

Sincerely,

Elizabeth Barbehenn, PhD
Research Analyst

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Deputy Director

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Medical Research Analyst

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Appendix 1. Deaths in patients where nefazodone was the primary suspect

Age	Sex	Adverse Event
52	M	Hepatorenal syndrome
54	F	Hepatic failure; liver transplant
57	F	Liver transplant
57	F	Hepatic failure; liver transplant
58	F	Hepatic failure
60	F	Hepatic failure
65	ND	Hepatic failure; liver transplant
80	F	Hepatic failure
87	M	Hepatorenal syndrome
ND	M	Hepatic failure; liver transplant
ND	M	Hepatic failure

ND= no data

Appendix 2. Non-fatal Hepatic Adverse Events Ascribed to Nefazodone

Age	Sex	Outcome	Adverse Event
14	F	Hospitalization	Liver function tests Nos Ab
16	F	Hospitalization	Hepatic failure; liver transplant
16	F	Life-threatening	Hepatic failure
19	F	Other	Liver function tests Nos Ab
30	F	Hospitalization	Hepatic failure
31	F	Hospitalization	Hepatic necrosis
33	F	Hospitalization	Hepatitis Nos
33	F	Life-threatening	Liver function tests Nos Ab
36	M	Hospitalization	Hepatitis Nos
37	F	Other	Hepatitis acute
39	F	Hospitalization	Hepatomegaly
40	M	Hospitalization	Hepatic failure
41	F	Hospitalization	Hepatic failure
42	F	Hospitalization	Hepatitis cholestatic
43	F	Hospitalization	Hepatitis Nos
46	F	Other	Liver function tests Nos Ab
46	M	Life-threatening	
48	M	Required intervention	Liver function tests Nos Ab
52	F	Hospitalization	Hepatitis Nos
52	F	Hospitalization	Hepatic failure
52	F	Hospitalization	Liver function tests Nos Ab
56	M	Hospitalization	Liver function tests Nos Ab
57	F	Life-threatening	Hepatic failure
57	F	Disability	Hepatitis Nos
60	F	Hospitalization	Hepatic failure
62	F		Liver function tests Nos Ab
68	M	Required intervention	Hepatitis Nos
ND	M	Hospitalization	Hepatic failure; hepatorenal failure
ND	F	Hospitalization	Liver function tests Nos Ab
ND	F	Hospitalization	Hepatitis Nos
ND	M	Disability	Hepatitis Nos
ND	ND	Hospitalization	Liver function tests Nos Ab
ND	M	Hospitalization	Hepatitis; liver function tests Nos Ab
ND	M	Hospitalization	Hepatocellular damage
ND	F	Hospitalization	Hepatic necrosis; liver transplant
ND	F	Hospitalization	Hepatic failure; liver transplant
ND	M	Hospitalization	Hepatic disorder Nos
ND	M	Hospitalization	Hepatic failure
ND	F	Hospitalization	Hepatitis cholestatic
ND	M	Hospitalization	Liver function tests Nos Ab
ND	M	Life-threatening	Liver function tests Nos Ab
ND	ND	Hospitalization	Liver function tests Nos Ab

ND= no data

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Public Citizen's Health Research Group

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To:	Mark B. McClellan, MD, PhD	**From:**	Marie Davis, Office Manager
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Fax:	(301) 443-3100	**Date:**	03/06/03
Re:	Petition	**CC:**	Dockets Management Branch (301) 827-6870

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comments:

Dr. McClellan:

Please find attached Public Citizen's petition to remove Serzone (nefazodone) from the market, effective immediately. Please do not hesitate to contact me if you have any questions. Thank you.

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