Public Citizen

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

Mark B. McClellan, M.D., Ph.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

October 29, 2003

Dear Commissioner McClellan:

Public Citizen, a nationwide consumer organization with a membership of more than 125,000 people, wishes to supplement its March 6, 2003 petition[1] (docket number 03P-0090), which called for the banning of the uniquely dangerous antidepressant drug Serzone (nefazodone; manufactured by Bristol-Myers Squibb Company) due to liver toxicity. As you are no doubt aware, Canada made the decision to ban Serzone on October 2, 2003, leaving the U.S. once again lagging behind other countries in drug safety.

Our original petition cited "53 cases of liver injury including 21 cases of liver failure from which 11 people died" that had been reported to the Food and Drug Administration (FDA). Even though Serzone had already been removed from the market in Europe and Scandanavia due to its hepatic toxicity,[2] your response to us of September 4, 2003 indicated that you had not as yet reached a decision on our petition "because it raises complex issues requiring extensive review and analysis by FDA officials."[3]

Canada has now joined Europe and Scandanavia in the removal of Serzone from the market because of Serzone's association with "hepatic adverse events such as jaundice, hepatitis and hepatocellular necrosis".[4] A "Dear Health Care Professional" letter, dated October 2, 2003, on the Health Canada website states that there were 51 Canadian reports of hepatotoxicity as of December 2002 "ranging from no symptoms to transplantation from which one patient died."

Our March 2003 petition covered the period from the time of Serzone's launch in December 1994 through March 31, 2002. We have now updated that analysis to cover the subsequent time period, April 1, 2002 through May 12, 2003. During that period, FDA adverse event data recorded an additional 9 deaths, for a total

[1] http://www.citizen.org/publications/release.cfm?ID=7233
[2] BMS to withdraw nefazodone in Europe. Scrip January 15, 2003; No 2815, p.21.
[3] Axelrad JA. Letter to SM Wolfe. Food and Drug Administration, September 4, 2003.
[4] http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/bms_nefazodone_2_hpc_e.pdf

03P-0090 SUP 1

of 20 reports of death due to liver failure in people using Serzone. The mounting number of deaths from liver failure from a drug with no unique efficacy strongly argues for the removal of the drug from the market.

New Data from the FDA Adverse Event Reports Database
We employed the same basic search criteria as in our March 6, 2003 petition. We searched the FDA's Adverse Event Reports (AERS) database for the drug names Serzone, nefazodone, Nefadar, and Dutonin listed as the Primary Suspect for the adverse reaction. Among these, we report only those with liver toxicity, identified by using the search terms hepat* and liver* for the adverse reaction ("Preferred Term") (see following Table).

Reports of Liver Toxicity Serzone Reported to the FDA

	Time period		
	12/94-3/02	4/02-5/03*	Total
Duration (years)	7.3	1.1	8.4
Hospitalization	29	12	41
Liver failure	22	33	55
Transplants	7 (4 died)	5 (2 died)	12
Any liver injury	53	41	94
Death from liver injury	11	9	20

* See the Appendix for a detailed list of these hepatic adverse events.

During the year between April 2002 and May 2003, there were an additional 41 cases of liver toxicity, including 9 deaths and 5 liver transplants. These numbers compare with 11 deaths and 7 transplants during the 7 years covered in our original petition. The most recent reporting period also included 12 hospitalizations and 33 cases of liver failure (there is some overlap between these last two categories). A total of 94 liver injuries, including 55 cases of liver failure and 20 deaths have now been reported to the FDA. Note the increase in the per cent of adverse event reports that are liver failure: 33/41 (80%) for the earlier period vs. 22/53 (42%) in the later period despite the addition of a Black Box warning for hepatotoxicity added in January 2002.[5] We emphasize that these are only the reported cases, which are typically estimated to be, at most, 10% of cases; thus, one must multiply by 10 to get an estimate that is closer to the actual number.

Nine deaths in the AERS database, in addition to the 20 in the table above, were listed as "death unexplained."

International Response to Cases of Liver Injury
Since our petition, Turkey has withdrawn Serzone from the market because of the possibility of acute hepatic failure. The decision was based on data received

[5] http://www.fda.gov/medwatch/SAFETY/2002/safety02.htm#serzon

by the Ministry of Health, worldwide developments, and the availability of alternative antidepressants on the market.[6]

In January 2003, Health Canada issued a report focused on the hepatobiliary adverse reactions of nine of the newer serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine). Serzone (nefazodone) had more suspected hepatobiliary adverse reaction reports than the 8 others, even though all but 3 have been marketed for more time. It was also the only one that had resulted in liver transplants.[7]

The World Health Organization (WHO) database (68 participating countries examined through June 2002) was analyzed for severe adverse reactions for seven serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline).[8] The authors used a statistical method that detects unexpectedly high rates of reports for the combination of particular adverse reactions and particular drugs. Looking specifically at hepatic injury (hepatitis, hepatic failure, and hepatic necrosis) in this group of seven serotonin reuptake inhibitors, only Serzone showed a statistically significant higher-than-expected rate of hepatic adverse reaction reports "in accordance with the findings in other studies."

Cases of Liver Injury from the Literature

Since our petition was filed, there has been a report in the literature, evidently not in the FDA database (as judged by gender and age characteristics), of two additional patients taking only Serzone who developed liver toxicity: a 61 year-old female who required a liver transplant and a 46 year-old male who required prolonged hospitalization.[9]

Difficulties in the Safe Prescribing of Serzone

Metabolism

Serzone is both metabolized by and inhibits a key drug-metabolizing enzyme in the liver (CYP 3A4). This inhibition can result in greater-than-expected increases in plasma drug levels of Serzone as drug doses are increased, producing unexpected toxicity. In addition to interfering with its own metabolism, Serzone also interferes with the metabolism of many other drugs. Some of these interactions have never been studied or have been studied using only a single

---

[6] Bristol Myers Squibb's 'Serzone' [nefazodone] is to be suspended in Turkey. Reactions; April 12, 2003;No. 946; p.2.

[7] Murty M, Morawiecka I, Sharma S. Suspected hepatobiliary adverse reactions to the newer antdepressants that affect serotonin neurotransmission. Canadian Adverse Drug Reaction Newsletter January 2003;13:1-3. http://www.hc-sc.gc.ca. Accessed October 16, 2003.

[8] Spigset O, Hagg S, and Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: data from the World Health Organization (WHO) database of adverse reactions. International Clinical Psychopharmacology 2003;18:157-161.

[9] Tzimas GN, Dion B, and Deschenes M. Early onset, nefazodone-induced fulminant hepatic failure. American Journal of Gastroenterology. 2003;98:1663-1664.

dose of the other drug. Information in the label indicates that some drugs require a washout before Serzone can be given, some require dose adjustment, and some are contraindicated.[10] However, the complexity of the interactions and the gaps in the knowledge base have meant that even a careful analysis of all drugs a patient is taking cannot guarantee safety. Furthermore, toxicity can occur in patients not taking any other drugs; the two cases in the literature cited above occurred in patients taking *only* Serzone and within 4 weeks of starting drug treatment, much too early to have been prevented by liver function test monitoring.

Diagnosing liver toxicity

The difficulty in diagnosing liver toxicity prior to major liver toxicity is reflected in Serzones's label (Warnings section) which states, "Although some reports described dark urine and nonspecific symptoms . . . other reports did not describe the onset of clear prodromal [early] symptoms prior to the onset of jaundice." Under the label's "Information for Patients," physicians are advised to discuss with patients the fact that, "At present, there is no way to predict who is likely to develop liver failure." This is not very comforting when liver damage can develop so quickly and can be fatal.

Although Serzone's label states that, "The physician may consider the value of liver function testing," it also adds that, "Periodic serum transaminase [liver function] testing has not been proven to prevent serious injury." As a result, there is no means available to reliably monitor and protect patients' health.

Conclusions

We found almost as many deaths from liver failure reported in the last 14 months we examined as in the 7 previous years (9 vs. 11). (As mentioned, these numbers likely need to be multiplied by 10 due to under-reporting.) This sorry record occurred despite the fact that, according to an analysis by the Agency for Health Care Policy and Research, the newer antidepressants (a class that includes Serzone) are considered no more efficacious than older antidepressants.[11]

Two independent groups have recently examined adverse event databases (Health Canada and WHO). Of the seven serotonin reuptake inhibitors looked at in the WHO database and the nine looked at in the Canadian database, *only Serzone was associated with an increased risk for serious hepatic injury.* Based on this increased risk of hepatic injury, Canada has now joined Europe and Scandanavia in deciding to remove Serzone from the market. The Bristol-Myers Squibb (Canada) "Dear Health Care Professional" letter makes the best case for removing Serzone, i.e., "*To date, no risk factor to predict patients who will develop irreversible liver failure with nefazodone has been identified. Also, no*

[10] Serzone label available at www.serzone.com; revised October 2002; accessed September 16, 2003.
[11] Agency for Health Care Policy and Research. Treatment of depression: newer pharmacotherapies. February 1999. Available at: http://www.ahcpr.gov. Accessed January 30, 2003.

clinical strategy, such as routine liver function tests, could be identified to reduce the risk of liver failure." [12] (Italics added)

There is no justification for the U.S. to continue marketing a drug that offers no advantage in efficacy over the existing drugs in its class (or even older antidepressants), and that has, among its class, unique and unpredictable toxicity. Serzone is extremely difficult to administer safely due to its dangerous interactions with many other drugs, its non-linear blood levels (blood levels increasing more than expected due to Serzone inhibiting its own metabolism), the impossibility of predicting who is at risk for liver toxicity, the difficulty in monitoring those most at risk, and the rapidity with which serious (and occasionally irreversible) liver damage can occur. We, therefore, reiterate our call to remove this drug from the market before more people are injured or killed.

Sincerely,

Elizabeth Barbehenn

Elizabeth Barbehenn, PhD
Research Analyst

Peter Lurie

Peter Lurie, MD, MPH
Deputy Director

Sidney Wolfe

Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group

[12] http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/bms_nefazodone_2_hpc_e.pdf

APPENDIX

Liver Adverse Event Reports from April 1, 2002 to May 12, 2003

Age/Sex	Adverse Event	Outcome
6/F	Hepatic failure	*Death*
21/F	Jaundice/GI disorder	Other
27/F	LFTs* abnormal	Unknown
30/F	Hepatic failure	Life-threatening
33/F	LFTs abnormal	Life-threatening
34/F	Hepatic disorder	Hospitalization
37/F	Hepatic failure	Hospitalization
39/F	Jaundice	Life-threatening
44/M	Hepatic failure Liver transplant	*Death*
44/F	Hepatic failure	Hospitalization
44/M	Hepatic failure Transplant surgery graft rejection	*Death*
44/M	Hepatic failure Complications of transplant	*Death*
46/F	Hepatic failure	Other
50/M	Hepatic failure	Life-threatening
50/M	Hepatic failure Hepatic necrosis	Other
51/M	Hepatic failure Liver transplant Hepatic necrosis	Hospitalization
57/F	Hepatic failure	*Death*
57/F	Hepatic failure	*Death*
57/F	Hepatic failure	Hospitalization
57/M	Hepatic cirrhosis	Other
60/F	Hepatic failure	Hospitalization
60/F	Hepatic failure	Hospitalization
67/M	LFTs increased	Other
74/M	Hepatic failure	Hospitalization
U/F	Hepatic failure	Other
U/F	Hepatic failure Liver transplant	Hospitalization
U/M	LFTs abnormal	Life-threatening

U/F	Hepatic failure	Other
U/F	Hepatic failure Liver transplant	Other
U/F	Hepatic failure	*Death*
U/F	Hepatic failure	Other
U/F	Hepatic failure	Hospitalization
U/F	Hepatic failure Liver transplant	Other
U/F	Hepatic failure	Other
U/F	Hepatitis acute Liver transplant	Hospitalization
U/M	Hepatic failure	Other
U/F	Hepatocellular damage	*Death*
U/M	Hepatic cirrhosis	Other
U/F	Hepatic failure	Other
U/F	Hepatic failure	Other
U/M	Hepatic failure	*Death*

U: unknown; *LFTs: Liver function tests (a measure of liver health)

1600 20th Street, NW
Washington, D.C. 20009-1001
Phone 202-588-1000
Fax 202-588-7798

Public Citizen 30 YEARS
Protecting Health, Safety & Democracy

Fax

To: Ryan, Dockets	**From:** Sidney Wolfe
Fax:	**Pages:** 8
Phone:	**Date:** 10/29/03
Re:	**CC:**

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

- **Comments:**