



0019 5 MAR 24 A9:45

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

March 24, 2005

Lester Crawford, DVM, Acting Commissioner
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Crawford,

Public Citizen, representing more than 150,000 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 pemoline (CYLERT®-Abbott Laboratories, and all generic versions), a stimulant drug for the treatment of attention deficit hyperactivity disorder (ADHD). In addition to having no demonstrated unique therapeutic benefit over other ADHD drugs such as methylphenidate, pemoline is known to have caused at least 21 cases of liver failure, including 13 resulting in liver transplantation or death. The drug's unfavorable risk to benefit ratio has led to its withdrawal in the United Kingdom and Canada, while the FDA instead opted for two separate changes to the pemoline label, in 1996 and 1999. A 2002 FDA study has clearly demonstrated that these labeling changes failed to increase monitoring for liver toxicity or ensure only second-line use of pemoline.¹ In light of this evidence of unique liver toxicity without evidence of unique therapeutic benefit, we contend that the only responsible course of action is to remove this dangerous drug from the market.

We are joined in our petition by Dr. Fredric Solomon, Clinical Professor of Psychiatry and Behavioral Sciences at the George Washington University School of Medicine, who in the course of 42 years of clinical experience has evaluated and cared for hundreds of patients with ADHD.

Serious Liver Toxicity

Pemoline, a central nervous system stimulant, was approved by the FDA for the treatment of ADHD on January 27, 1975. Last year, there were approximately 117,000 pemoline prescriptions filled in the U.S. However, reports of liver abnormalities appeared in U.S. clinical trials even before approval.^{2,3} The first reports were identified in a 1973 prospective study of pemoline in which there were 2 cases of liver toxicity out

2005P.0115

CP1

of approximately 600 patients receiving chronic therapy. Fatty liver deposits were identified at biopsy, and in both cases liver toxicity diminished when treatment was discontinued but then reappeared after the drug was resumed.³ A 1974 pemoline trial enrolling 288 children reported a 3.1% rate of abnormal liver function tests. Incorporating data from this and previous studies, the authors estimated that drug-induced liver enzyme abnormalities occurred in 1% to 2% of patients taking pemoline.⁴ Between the 1975 approval and 1996, there were 193 adverse drug reactions involving the liver ascribed to pemoline reported to the FDA which concerned youths under the age of 20.⁵ As of May 1996, there were 13 cases acute liver failure due to pemoline, 11 of which resulted in death or liver transplantation.⁶

Based on an analysis of three case reports of fatal liver failure, Berkovitch, *et al.* calculated in a 1995 study that pemoline caused a 45-fold increased risk for the development of fulminant liver failure in children (RR=45.3, 95% CI: 4.1-510, P<0.001).⁷ These findings prompted an FDA review by its Division of Pharmacovigilance and Epidemiology (DPE, now called the Office of Drug Safety) of the available case report data. While the DPE found flaws in the analysis by Berkovitch *et al.*, its own analysis yielded an estimated 16.8-fold increased risk of acute liver failure due to pemoline compared to the general population, assuming no underreporting. Given that adverse events are reported to the FDA about 10% of the time, the relative risk for acute liver failure could be closer to 168-fold. The DPE's medical officer who performed the analysis, Dr. David Graham, estimated an absolute risk of fulminant liver failure in pemoline users of 1 per 2,000, assuming that 10% of the actual cases had been reported.⁸

In a letter to Abbott dated February 20, 1996, the FDA concluded that pemoline had "an unfavorable risk to benefit ratio," and that it would be withdrawn from the market unless Abbott could provide a "satisfactory rationale" for keeping it on the market.⁹ Abbott responded by challenging the FDA's analysis in an argument that, according to the DPE, "seriously underestimated the true relative and absolute risk of fulminant hepatic failure associated with pemoline use."⁸ Nevertheless, Dr. Paul Leber, Director of the Division of Neuropharmacological Drug Products, allowed Abbott to continue marketing the drug. A black box warning was added to the labeling for pemoline in the United States in December 1996, and a "Dear Doctor" letter was mailed out from Abbott to all U.S. physicians. The warning stressed pemoline's liver toxicity and recommended that it should no longer be considered a first-line therapy for ADHD.⁶ This decision to make pemoline a second-line therapy was made without any clinical trials showing that it actually worked in patients who had failed to respond to a first-line therapy.

In a letter to Abbott dated June 14, 1996, Dr. Leber wrote:

You should be aware that serious consideration was given to the option of asking that Cylert be withdrawn from marketing.... Because uncertainties remain about the absolute level of risk, however, we believe that marketing may continue if, and only if, a good faith effort is made on your part to collect the data necessary to construct a more precise estimate of the absolute risk. This information can be

collected if you establish a registry that has the capacity to track patients given Cylert prospectively from the point at which treatment is initiated.¹⁰ (emphasis added)

Despite this strongly conditional warning, we are not aware that Abbott has ever created such a registry. Certainly, there is no evidence that the registry's findings have ever been published.

Recent Case Reports of Liver Toxicity

As liver failure cases continued to accumulate, the FDA addressed the issue with a stronger black box warning in June 1999. The 1999 warning label states that as of December 1998 there were 15 cases of acute liver failure due to pemoline reported to the FDA, 12 of which resulted in death or liver transplantation.¹¹ Although pemoline use has declined significantly since that time, a review of the FDA Adverse Event Reporting System (AERS) database since December 1998 reveals 15 additional reports of liver toxicity in which pemoline was the primary suspect drug (See Table 1). These include 6 cases of liver failure including 1 liver transplant. This means that since pemoline was marketed, 21 cases of liver failure, including 13 deaths or liver transplants, have been reported to the FDA. Because only 10% or so of adverse events are reported to the FDA, these are clearly underestimates of the true number of such cases.

Table 1. Adverse Drug Reaction Reports of Liver Toxicity Due To Pemoline Since 1999.

FDA Report Date	Age	Liver Toxicity	Outcome
01-Feb-99	9	Hepatitis	Hospitalization
01-Feb-99	6	Hepatic Failure	Hospitalization
01-Feb-99	14	Hepatic Failure	Hospitalization, Life-Threatening
26-Feb-99	Unknown	Hepatic Disorder Nonspecified	Unknown
26-May-99	42	Hepatic Failure	Life-Threatening, Required Intervention
08-Sep-99	29	Liver Fatty	Unknown
24-Sep-99	10	Hepatomegaly	Unknown
20-Jan-00	Unknown	Hepatic Disease Nonspecified	Unknown
10-Mar-00	29	Liver Fatty	Unknown
31-Jan-01	25	Hepatic Failure	Unknown
29-Mar-02	44	Hepatocellular Damage	Hospitalization
24-Feb-03	17	Autoimmune Hepatitis	Hospitalization
11-Aug-03	41	Hepatotoxicity	Required

			Intervention
25-Aug-03	39	Hepatic Failure	Hospitalization
26-Nov-03	36	Hepatic Failure	Liver Transplantation

Table 1. Adverse drug reaction reports to FDA AERS database in which pemoline is the primary suspect for liver toxicity, 1/1999-9/2004. Searches of the database were conducted using adverse effect terms "liver" and "hepat-."

Pemoline Withdrawn Abroad

While the United States has allowed Abbott to continue marketing the drug, other countries have taken more decisive action based on patient liver toxicity data collected predominantly from the U.S. In September 1997, the United Kingdom removed pemoline from the market. In its announcement that the drug would be banned, the Committee on Safe Medicines (CSM) wrote:

The evidence for the efficacy of pemoline in the treatment of hyperkinetic syndrome [ADHD] is limited and there is no good evidence from appropriate clinical trials that pemoline is effective in patients who have failed to respond to alternative drugs.

Since there is a significant risk of serious hepatic toxicity, which may prove fatal, the CSM considered that the risks of treatment with pemoline outweigh the benefits and the drug has therefore been withdrawn.¹²

The UK decision was based entirely on case reports of liver toxicity from the United States. In September 1999, the Canadian government reached a similar conclusion and removed pemoline from the market, reasoning that the drug's risks outweighed its benefits. According to Health Canada:

This conclusion was based on a number of considerations, the most important of which were: (a) despite explicit warnings in the product monograph and labeling information regarding the risk of severe liver damage, worldwide case reports of liver failure necessitating transplantation or resulting in death continued; (b) there is no evidence that liver damage caused by the drug is predictable or reversible; (c) other, safer treatment alternatives are available; and (d) a satisfactory response to the TPP's [Therapeutic Products Programme's] request for specific evidence to support the safety of the drug's continued use was not provided by the manufacturer.¹³

Pemoline's FDA Labeling Proven Ineffective

In June 1999, as U.S. reports of liver toxicity due to pemoline continued to accumulate, Abbott sent another "Dear Healthcare Provider" letter to U.S. physicians describing the FDA's newly revised black-box warning for pemoline. In addition to the 1996 warning

that pemoline should be shifted from first-line to second-line therapy for ADHD, the 1999 recommendations specified baseline monitoring of liver enzymes, repeated every two weeks thereafter, and obtaining informed consent for treatment from the patient.

A 2002 study by the FDA itself measured adherence to the various black box labeling recommendations. The study used a large health care company's administrative claims database, which included 1,308 patients who were newly prescribed pemoline from January 1998 to March 2000. While the recommendation that pemoline be used only as second-line therapy for ADHD had been in place since the 1996 label, only 237 patients (34%) were found to have received another ADHD drug prior to pemoline. Dividing the data into two six-month periods, before and after the June 1999 labeling change, the authors found that the new labeling had no measurable effect on liver enzyme testing rates. Twelve percent of pre-label change patients received baseline liver enzyme tests, compared to 11% of patients after the labeling change. The percentage of patients receiving *any* follow-up liver enzyme tests (the label recommended biweekly testing) was similarly low before and after the labeling change (9% pre-change vs. 12% post-change). The authors concluded that "labeling changes, including black-box warnings, had no measurable effect on compliance with the labeling recommendations for pemoline."¹

No Unique Therapeutic Role

Defenses of dangerous drugs such as pemoline often invoke arguments that there is some unique niche that the drug fills that justifies its remaining on the market. The main initial appeal of pemoline to clinicians was that it allowed once-a-day dosing, as opposed to multiple daily doses which might raise logistical problems especially for children in school during the day. However, due to the development of long-acting formulations of standard stimulant medications, this is no longer a unique characteristic.

Proponents of pemoline may claim that it has a lower abuse potential than other stimulant treatments for ADHD, and therefore, pemoline's unique therapeutic role may be for the treatment of ADHD where substance abuse is a concern. In reality this argument breaks down to two separate potential scenarios, each of which we will discuss here.

The first scenario posits that exposure to stimulants results in increased neurological sensitivity to the effects of the drugs, thereby increasing the risk of generalized drug abuse.¹⁴ If this were true, a stimulant with lower abuse potential might be less likely to put patients at such risk. However, stimulant treatment for ADHD does not appear to adversely affect either co-occurring substance abuse or the likelihood of future substance abuse. Two randomized controlled trials, one studying methylphenidate treatment of patients with ADHD and cocaine-dependence¹⁵ and the other studying pemoline for ADHD in substance-abusing adolescents,¹⁶ have shown that neither methylphenidate nor pemoline had an effect on co-occurring substance-abuse behavior. Similarly, the weight of the evidence suggests that stimulant treatment for ADHD does not lead to substance use or abuse later in life.¹⁴ In fact, a 2003 meta-analysis of seven

studies found that stimulant treatment of ADHD with methylphenidate or amphetamine actually reduced the risk of substance use disorders 1.9-fold,¹⁷ down to levels within normal population risks.¹⁸

The second scenario refers specifically to the potential for the abuse of the stimulants themselves. Pemoline, like the other stimulant treatments for ADHD, is a controlled substance. While the potential for the abuse and diversion of methylphenidate and amphetamines is better established, pemoline is not devoid of risk for abuse. The FDA-approved labeling for pemoline (CYLERT) warns that "the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT."¹⁹ Furthermore, concerns about abuse and diversion with older immediate-release stimulant tablets have been eased with the arrival of newer stimulant preparations. Concerta, for example, is a once-daily extended-release form of methylphenidate in the form of a paste, which cannot be ground up or snorted. The American Academy of Child and Adolescent Psychiatry recommends these newer preparations, not pemoline, as the most suitable for adolescents with ADHD who are at risk for abusing or diverting their stimulant medications.²⁰

Relatively safe and effective drug treatments exist for ADHD. Methylphenidate and dextroamphetamine are generally considered the drugs of choice, and patients with ADHD who fail to respond to one of these two drugs are rare.^{21,22} There is no good evidence from appropriate clinical trials that pemoline has a unique therapeutic benefit for the treatment of ADHD, or that it is effective in patients who have failed to respond to first-line drugs. Indeed, parameters for stimulant treatment of ADHD issued by the American Academy of Child and Adolescent Psychiatry do not recommend the use of pemoline under any circumstances.²⁰

Conclusions

In the late 1990's, as evidence of pemoline's liver toxicity mounted, the UK and Canada made the decision that it was in the interest of public health to withdraw pemoline from the market because its risk outweighed its benefit. The FDA gave strong consideration to the withdrawal of the drug, but instead elected to allow sales of pemoline as long as the sponsor made a good faith effort to gather more safety data and the label was changed. However, Abbott does not appear to have carried out the prospective patient registry that was a condition for the drug's continued marketing, and the labeling changes made have had no measurable effect on ensuring safe use of pemoline. Proponents have never submitted any compelling evidence that pemoline is effective in patients for whom alternative drugs for ADHD are not effective. In the absence of data demonstrating that pemoline has any unique therapeutic benefit over other, safer drugs for the treatment of ADHD, there is no responsible basis for keeping this unacceptably dangerous drug on the market.

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.

Sincerely,



Nicholas Stine
Research Associate



Peter Lurie, MD, MPH
Deputy Director



Sidney M. Wolfe, MD
Director

Public Citizen's Health Research Group



Fredric Solomon, MD*

*Dr. Solomon practices Child, Adolescent and Adult Psychiatry in Washington, DC. He is Clinical Professor of Psychiatry and Behavioral Sciences at the George Washington University School of Medicine. His former positions include: Director, Division of Mental Health and Behavioral Medicine at the Institute of Medicine of the National Academy of Sciences; Associate Professor of Psychiatry and Neurology at Howard University College of Medicine; and Consultant to the National Institute of Mental Health. He was elected by child psychiatrists in the Washington, DC area for three terms as their delegate to the Assembly of the American Academy of Child and Adolescent Psychiatry. In the course of 42 years of clinical experience, Dr. Solomon has evaluated and cared for hundreds of patients who suffered from ADHD.

- ¹ Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A Study of Compliance With FDA Recommendations for Pemoline (Cylert). *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002 July;41(7):785-790.
- ² Gilbert JG, Donnelly KJ, Zimmer LE, Kubis JF. Effect of Magnesium Pemoline and Methylphenidate on Memory Improvement and Mood in Normal Aging Subjects. *International Journal of Aging and Human Development*. 1973;4:35-51.
- ³ Tolman KG, Freston JW, Berenson MM, Sannella JJ. Hepatotoxicity Due to Pemoline. Report of Two Cases. *Digestion*. 1973;9(6):532-9.
- ⁴ Page JG, Bernstein JE, Janicky RS, Michelli FA. A Multi-Clinic Trial of Pemoline in Childhood Hyperkinesia. Clinical Use of Stimulant Drugs in Children: Proceedings of a Symposium Held at Key Biscayne, Florida, 5-8 March 1972. Conners CK, ed. New York: Excerpta Medica, 1974, pp 98-124.
- ⁵ Safer DJ, Zito JM, Gardner JF. Pemoline Hepatotoxicity and Postmarketing Surveillance. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40:622-629.
- ⁶ Pizzuti D. Dear Doctor Letter, Cylert. Abbott Laboratories, Abbot Park, IL, December 1996.
- ⁷ Berkovitch M, Pope E, Phillips J, Koren G. Pemoline-Associated Fulminant Liver Failure: Testing the Evidence for Causation. *Clinical Pharmacology & Therapeutics*. 1995;57:696-698.
- ⁸ Graham DJ. Fulminant Hepatic Failure with Pemoline (Cylert). FDA Memorandum from Medical Officer, Epidemiology Branch (HFD-733), to Director, Division of Neuropharmacologic Drug Products (HFD-120). April 17, 1996. Accessed January 12, 2005, at http://www.fda.gov/cder/foi/nda/96/1996-016832a_s013.pdf.
- ⁹ Leber PD. Letter from Director, Division of Neuropharmacologic Drug Products, FDA, to Abbott Laboratories, February 20, 1996. (Referenced in Leber, PD. Decision on Cylert Hepatotoxicity Action. Memorandum from Director, Division of Neuropharmacologic Drug Products (HFD-120). October 29, 1996. Accessed January 12, 2005, at http://www.fda.gov/cder/foi/nda/96/1996-016832a_s014.pdf).
- ¹⁰ Leber PD. Letter from Director, Division of Neuropharmacologic Drug Products, FDA, to Abbott Laboratories. June 14, 1996. Accessed January 12, 2005, at http://www.fda.gov/cder/foi/nda/96/1996-016832a_s013.pdf.
- ¹¹ Pizzuti D. Dear Health Care Professional Letter, Cylert. Abbott Laboratories, Abbot Park, IL, June 1999.
- ¹² Anonymous. Volital (Pemoline) Has Been Withdrawn. *Current Problems in Pharmacovigilance*. Medicines and Healthcare Products Regulatory Agency (MHRA) and Committee on Safe Medicines (CSM). UK Department of Health. 1997;23:9-12.
- ¹³ Hogan V. Pemoline (Cylert) Market Withdrawal. *Canadian Adverse Drug Reaction Newsletter*. 2000 January;10(1):3.
- ¹⁴ Mannuzza S, Klein RG, Moulton JL 3rd. Does Stimulant Treatment Place Children at Risk for Adult Substance Abuse? A Controlled, Prospective Follow-Up Study. *Journal of Child and Adolescent Psychopharmacology*. 2003 Fall;13(3):273-82.
- ¹⁵ Schubiner H, Saules KK, Arfken CL, Johanson CE, Schuster CR, Lockhart N, Edwards A, Donlin J, Pihlgren E. Double-Blind Placebo-Controlled Trial of Methylphenidate in the Treatment of Adult ADHD Patients with Comorbid Cocaine Dependence. *Experimental and Clinical Psychopharmacology*. 2002 August;10(3):286-94.
- ¹⁶ Riggs PD, Hall SK, Mikulich-Gilbertson SK, Lohman M, Kayser A. A Randomized Controlled Trial of Pemoline for Attention-Deficit/Hyperactivity Disorder in Substance-Abusing Adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004 April;43(4):420-9.
- ¹⁷ Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does Stimulant Therapy of Attention-Deficit/Hyperactivity Disorder Beget Later Substance Abuse? A Meta-Analytic Review of the Literature. *Pediatrics*. 2003 January;111(1):179-85.
- ¹⁸ Faraone SV, Wilens T. Does Stimulant Treatment Lead to Substance Use Disorders? *Journal of Clinical Psychiatry*. 2003;64 Suppl 11:9-13.
- ¹⁹ CYLERT (pemoline). *Physicians' Desk Reference*. 59th Ed. Montvale, NJ.: Thomson PDR, 2005. 419.
- ²⁰ American Academy of Child and Adolescent Psychiatry. Practice Parameters for the Use of Stimulant Medications in the Treatment of Children, Adolescents, and Adults. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002 February;41(2) Suppl:26S-49S.
- ²¹ Elia J, Ambrosini PJ, Rapoport, JL. Treatment of Attention-Deficit-Hyperactivity Disorder. *New England Journal of Medicine*. 1999 March 11;340(10):780-8.
- ²² Elia J, Borcharding BG, Rapoport JL, Keysor CS. Methylphenidate and Dextroamphetamine Treatments of Hyperactivity: Are There True Nonresponders? *Psychiatry Research*. 1991 February;36(2):141-55.