

U.S. Food and Drug Administration
Warnings on “Attention Deficit
Hyperactivity Disorder”
(ADHD) Drugs



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U.S. Food and Drug Administration Warnings on “Attention Deficit Hyperactivity Disorder” (ADHD) Drugs

Since the mid-1980's, the Citizens Commission on Human Rights (CCHR) has campaigned against the indiscriminate and ever-growing drugging of school children diagnosed with Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD) with stimulant drugs.

Stimulants such as Ritalin and Dexedrine are in the same U.S. Drug Enforcement Administration (DEA) classification as cocaine, yet millions of children are prescribed these drugs on a daily basis. The so-called “newer” stimulant drugs to treat these invented disorders have proven just as dangerous.

Following is a brief summary of just the warnings on stimulant drugs issued since late 2004:

STIMULANT DRUG WARNINGS

- On 17 December 2004, the U.S. FDA required a new warning be added to the packaging of the “ADHD” drug, Strattera. The FDA noted, “The labeling warns that severe liver damage may progress to liver failure resulting in death or the need for a liver transplant in a small percentage of patients.”
- On 29 June 2005, the FDA announced labeling changes for Concerta and other methylphenidate products (stimulant based drugs) used to treat attention deficit/hyperactivity disorder to include, “psychiatric events such as visual hallucinations, suicidal ideation, psychotic behavior, as well as aggression or violent behavior.”
- On 29 September 2005, the U.S. FDA issued a Public Health Advisory entitled “Suicidal Thinking in Children and Adolescents Being Treated with Strattera (Atomoxetine).” (Strattera is an ADHD drug.) The advisory states that the FDA has directed the labeling of Strattera to include both a boxed warning and additional warning statements that alert health care providers to an increased risk of suicidal thinking in children and adolescents.

- On 24 October 2005, the Associated Press announced that the FDA had withdrawn its approval for the ADHD drug Cylert due to the drug causing liver problems, including death.

FDA Public Health Advisory, 17 December 2004

“New Warning for Strattera”



FDA Talk Paper

T04-60
December 17, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

New Warning for Strattera

The Food and Drug Administration (FDA) is advising health care professionals about a new warning for Strattera, a drug approved for attention deficit hyperactivity disorder (ADHD) in adults and children. The labeling is being updated with a bolded warning about the potential for severe liver injury following two reports (a teenager and an adult) in patients who had been treated with Strattera for several months, both of whom recovered.

The labeling warns that severe liver injury may progress to liver failure resulting in death or the need for a liver transplant in a small percentage of patients. The labeling also notes that the number of actual cases of severe liver injury is unknown because of under-reporting of post-marketing adverse events.

The bolded warning indicates that the medication should be discontinued in patients who developed jaundice (yellowing of the skin or whites of the eyes) or laboratory evidence of liver injury.

Strattera has been on the market since 2002 and has been used in more than 2 million patients. In clinical trials of 6000 patients, no signal for liver problems (hepatotoxicity) had emerged.

FDA has asked the manufacturer to add a bolded warning about severe liver injury to the labeling. Eli Lilly has agreed to alert health care professionals about the new information in a Dear Health Professional letter. The company will also update the patient package insert with information about the signs and symptoms of liver problems, which include:

- Pruritus (Itchy skin)
- Jaundice
- Dark urine
- Upper right-sided abdominal tenderness
- Or unexplained "flu-like" symptoms

Health care professionals are encouraged to report any unexpected adverse events associated with Strattera directly to Eli Lilly, Indianapolis, Ind., at 1800-LillyRx or to the FDA MedWatch program at 1800-FDA-1088. The MedWatch form is available online at <http://www.fda.gov/medwatch/safety/3500.pdf> for download by mail (or fax, 1800-FDA-0178) to MedWatch, HFD-410, FDA, 5600 Fishers Lane, Rockville, Md. 20857.

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FDA Advisory Committee, 29 June 2005

“Concerta Psychiatric Safety Labeling”

J&J Concerta Psychiatric Safety Labeling, Cardiovascular Events Are Topics For Cmte.

FDA intends to include language concerning psychiatric adverse events in labeling for Johnson & Johnson's attention deficit/hyperactivity disorder therapy **Concerta** and other methylphenidate products.

"Post-marketing reports received by FDA regarding Concerta and other methylphenidate products include psychiatric events such as visual hallucinations, suicidal ideation, psychotic behavior, as well as aggression or violent behavior," the agency said in briefing documents for its June 30 Pediatric Advisory Committee meeting.

"We intend to make labeling changes describing these events," FDA said.

FDA scheduled the meeting to discuss adverse event reporting for methylphenidate products, as required by the Best Pharmaceutical for Children Act.

In addition, the agency plans to "examine the other stimulant products approved for ADHD, specifically the amphetamine products, and atomoxetine (Lilly's **Strattera**)...to determine if they are associated with these adverse events," FDA said. Strattera is not a stimulant.

FDA is currently examining the post-marketing adverse event reports for the products and hopes to present the analysis to the Pediatric Committee in early 2006.

"Given that both methylphenidates and amphetamines are stimulants used in the treatment of ADHD, it is important we evaluate both stimulant classes in order to avoid potential switching from one class to the other based on incomplete safety assessments," FDA explained.

FDA will ask the committee to comment on its plan for evaluating psychiatric events with the ADHD products.

The agency would also like to know if there is any other information it should provide to the public while developing the information on psychiatric adverse events with the stimulants and Strattera.

The committee will also discuss cardiovascular events with ADHD drugs.

FDA previously strengthened Shire's ADHD therapy **Adderall XR's** "black box" warning to note that the agent "may cause sudden death and serious cardiovascular adverse events."

Meanwhile, Canadian health authorities suspended marketing of Adderall XR due to the adverse events after being presented with a "thorough" review of safety information from Shire.

FDA, however, said it "believes that it is not yet possible to determine whether these events, especially the more serious ones, are causally associated with these treatments."

The agency said it is pursuing "additional means to better characterize the cardiovascular risks for all drug products approved for ADHD."

FDA is considering population-based pharmacoepidemiologic studies, long-term safety trials and other targeted CV risk studies.

"While FDA pursues these additional potential options, the agency may consider advising patients and physicians of our ongoing efforts and the reasons for them," the agency said.

To watch a webcast of this meeting, click the button below. To arrange for live videoconferencing, or to order videotapes & DVDs, email webcasthelp@elsevier.com or call 800-627-8171.

Posted: Wednesday, June 29, 2005

FDA Public Health Advisory, 29 September 2005

“Suicidal Thinking in Children and Adolescents
Being Treated with Strattera”



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Public Health Advisory Suicidal Thinking in Children and Adolescents Being Treated With Strattera (Atomoxetine)

Today the Food and Drug Administration (FDA) directed Eli Lilly and Company (Lilly), the manufacturer of Strattera (atomoxetine), to revise the labeling for this product to include a boxed warning and additional warning statements that alert health care providers to an increased risk of suicidal thinking in children and adolescents being treated with this drug. FDA also informed Lilly that it has determined that a Patient Medication Guide (MedGuide), which will advise patients of the risks associated with Strattera and precautions that can be taken, should be distributed to patients when Strattera is dispensed.

Strattera is approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric and adult patients.

The increased risk of suicidal thinking for this drug was identified in a combined analysis of 12 short-term (6-18 weeks) placebo-controlled trials (11 in ADHD and 1 in enuresis [bedwetting]). These 12 trials involved a total of over 2200 patients, including 1357 receiving Strattera and 851 receiving placebo. The analysis showed a greater risk of suicidal thinking during the first few months of treatment in those receiving Strattera. The average risk of suicidal thinking was about 4 per thousand patients treated with Strattera compared to no events in placebo-treated patients. There was 1 suicide attempt among these approximately 2200 patients, occurring in a patient treated with Strattera. Based on these data, FDA has determined that the following points are appropriate for inclusion in the boxed warning:

- Strattera increases the risk of suicidal thinking in children and adolescents with ADHD.
- Anyone considering the use of Strattera in a child or adolescent for ADHD must balance the increased risk of suicidal thinking with the clinical need for the drug.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidal thinking or behaviors, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate changes or concerning behaviors with the prescriber.

Pediatric patients being treated with Strattera should be closely observed for clinical worsening, as well as agitation, irritability, suicidal thinking or behaviors, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This monitoring should include daily observation by families and caregivers and frequent contact with the physician.

In addition a MedGuide is being prepared for Strattera to provide directly to patients and their families and caregivers information about the increased risk of suicidal thinking in children and adolescents prescribed Strattera. The MedGuide is intended to be distributed by the pharmacist with each prescription or refill of a medication.

A similar analysis in adult patients treated with Strattera for either ADHD or major depressive disorder (MDD) found no increased risk of suicidal ideation or behavior with use of Strattera.

FDA plans to work closely with Lilly to optimize the safe use of this drug and implement the proposed labeling changes and other safety communications in a timely manner.

FDA Public Health Advisory, 24 October 2005

Alert for Healthcare Professionals
Pemoline Tablets and Chewable Tablets
(marketed as Cylert)



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Regulatory Guidance

CDER Calendar

Specific Audiences

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Alert for Healthcare Professionals Pemoline Tablets and Chewable Tablets (marketed as Cylert)

FDA ALERT [10/2005]: Liver Injury Risk and Market Withdrawal

The Agency has concluded that the overall risk of liver toxicity from Cylert and generic pemoline products outweighs the benefits of this drug. In May 2005, Abbott chose to stop sales and marketing of Cylert in the U.S. All generic companies have also agreed to stop sales and marketing of this product (Pemoline tablets and chewable tablets). Cylert is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). This product is considered second line therapy for ADHD because of its association with life threatening hepatic failure (see **BOXED WARNING in product label and patient package insert, available at** http://www.fda.gov/cder/foi/label/2003/016832s022_017703s018lbl.pdf)

FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program at 1-800-FDA-1088 or <http://www.fda.gov/medwatch/report/hcp.htm>

Recommendations

Health Care Professionals who prescribe Cylert, or any of its generics, should transition their patients to an alternative therapy. Cylert will remain available through pharmacies and wholesalers until supplies are exhausted; no additional product will be available.

Data Summary

FDA is aware of 13 reports of liver failure resulting in liver transplant or death, usually within four weeks of onset of signs and symptoms of liver failure. Although the absolute number of reported cases of liver failure with pemoline is not large, the reporting rate for liver failure with

pemoline is 10 to 25 times greater than the background rate of liver failure in the general population.

Despite diminished use of Cylert and generic pemoline products since the addition of the boxed warning in 1999 (about 1/5 the number of prescriptions now compared to before the boxed warning) and restrictive labeling (e.g., boxed warning, second line therapy, Medication Guide), a risk of liver failure remains (FDA is aware of 1 new case of pemoline-associated liver failure since the introduction of the boxed warning in 1999). Given the availability of multiple other drug treatments for ADHD, including 1 that is not scheduled and several products that can be given once a day, FDA has concluded that the risk of liver failure with this drug outweighs the potential benefits.

Cylert Labeling Information

http://www.fda.gov/cder/foi/label/2003/016832s022_017703s018lbl.pdf

Report serious adverse events to FDA's MedWatch at 1-800-FDA-1088; or
<http://www.fda.gov/medwatch/report/hcp.htm>

Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-827-4570
Druginfo@cdcr.fda.gov

CITIZENS COMMISSION ON HUMAN RIGHTS

The Citizens Commission on Human Rights (CCHR[®]) was co-founded in 1969 by the Church of Scientology and Dr. Thomas Szasz, Professor of Psychiatry Emeritus, to investigate and expose psychiatric violations of human rights and to clean up the field of mental healing. Today, it has more than 130 chapters in 34 countries. Its board of advisors includes doctors, lawyers, educators, artists, business professionals and civil and human rights representatives.

CCHR has inspired and contributed to many hundreds of reforms by testifying before legislative hearings and conducting public hearings into psychiatric abuse, as well as by working with media, law enforcement and public officials the world over.

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