

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number: 17703/S011**

**Trade Name: CYLERT CHEWABLE TABLETS**

**Generic Name: PEMOLINE**

**Sponsor: ABBOTT LABORATORIES**

**Approval Date: 4/11/96**

**Indication(s): TREATMENT OF ATTENTION DEFICIT  
DISORDER**

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION: 17703/S011**

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Final Printed Labeling		X		
Medical Review(s)				X
Chemistry Review(s)				X
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Pharmacology Review(s)				X
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Clinical Pharmacology				X
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Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: 17703/S011**

**APPROVAL LETTER**

NDA 16-832 / S-013  
NDA 17-703 / S-011

APR 11 1996

Abbott Laboratories  
Attention: Samuel A. Bohannon  
100 Abbott Park Road  
Abbott Park, IL 60064-3500

APR 11 1996  
08

Dear Mr. Bohannon:

Please refer to your January 5, 1996, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cylert (pemoline) Tablets and Chewable Tablets.

These supplemental applications provide for updated labeling with changes to the Overdosage section as follows:

*(Note: Additions are shaded in "redline font." Deletions are in "strikeout font.")*

...tachycardia, hypertension and mydriasis. Consult with a Certified Poison Control Center regarding treatment for up to date guidance and advice. Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present.

Gastric contents may be evacuated by gastric lavage. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Chlorpromazine has been...

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective for use as recommended in the final printed labeling submitted on January 5, 1996. Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,

PS/

4/8/96

APR 11 1996  
08

Paul Leber, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Original NDAs 16-832, 17-703

HFD-120/Div. files

HFD-120/CSO/S.Hardeman

HFD-120/Laughren/Mosholder

HFD-101/L.Carter (with labeling)

DISTRICT OFFICE

HF-2/medwatch (with labeling)

HFD-80 (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613 (with labeling - Only for applications with labeling.)

*/S/* 4-5-96  
*/S/*  
4/4/96

Final: April 4, 1996

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APPROVAL

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 17703/S011**

**ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE**



**ABBOTT**

**ORIGINAL**

NDA NO. 17-703 REF. NO. SLR-011  
NDA SUPPL FOR Labeling

**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
Abbott Park, Illinois 60064-3500

January 5, 1996

**NDA SUPPLEMENT**



Paul Leber, M.D.  
Division of Neuropharmacological Drug Products  
Woodmont II, HFD-120  
Food and Drug Administration  
1451 Rockville Pike  
Rockville, MD 20852

APPROVED FOR  
[illegible]

*No changes  
other than  
those specific  
by sponsor  
JS/  
4/4/96*

**Re: Cylert® Chewable Tablets (pemoline)  
NDA 17-703**

**SPECIAL SUPPLEMENT  
CHANGES BEING EFFECTED**

Dear Dr. Leber:

Further to your letter dated August 11, 1995, and my conversation with Steve Hardeman on January 4, 1996, this supplement is being submitted to provide updated labeling. The changes in this letter will be implemented in all finishing operations after February 11, 1996.

This submission contains the following:

- 1) Edited/highlighted copies of draft package inserts showing the revisions. The package insert has been revised prior to the current draft with the following changes:
  - "Power" was corrected to "Powder" in the **DESCRIPTION** Section (first line below the structure).
- 2) In the archival copy are fifteen copies of final printed labeling for Cylert® (03-4633-R17-Rev. Dec., 1995), ten of which are mounted on heavy weight paper. One copy of this package insert is provided in the review copy.

*1/23/96 Noted  
this is in response to our letter of  
8/11/95 requesting changes in the  
overdose section of labeling  
/S/*



If there are any questions regarding this submission, please call me at the number listed below.

Sincerely,

Samuel A. Bohannon  
Product Manager, PPD Regulatory Affairs  
D-491, AP6B-1, (708) 937-0859  
Fax: (708) 937-8002

SAM:tl  
Enclosure

**Copy of the cover letter to:**

Mr. Steven Hardeman, Project Manager  
Division of Neuropharmacological Drug Products  
Woodmont II, HFD-120  
Food and Drug Administration  
1451 Rockville Pike  
Rockville, MD 20852

NDA 16-832  
NDA 17-703

Abbott Pharmaceutical Products Division  
Abbott Laboratories  
Attention: Samuel A. Bohannon  
100 Abbott Park Road  
Abbott Park, IL 60064-3500

JUN 14 1996

Dear Mr. Bohannon:

Please refer to your new drug applications for Cylert (pemoline) Tablets and Chewable Tablets.

Refer also to your March 14, 1996, submission responding to our letter of February 20, 1996, regarding hepatic failure associated with pemoline therapy. Your submission provided a review of data on hepatic failure with Cylert use and contained proposals for labeling changes and a Dear Doctor letter.

We have reviewed your analyses and estimates of the incidence of acute liver failure that is associated with the use of Cylert. While we are mindful of the uncertainties that are associated with any estimate that may be generated, we are persuaded that the absolute risk (as well as the risk relative to that associated with competing products) of liver failure leading to transplantation and/or death, even if it is as low as you argue it might be, is still too high to be tolerated in a marketed drug product that is being recommended, without qualification, as a treatment for Attention Deficit Hyperactivity Disorder.

Our analyses of the data available indicate that the relative risk of acute liver failure is considerably higher among Cylert treated patients than among those receiving any other approved treatment. Admittedly, the absolute number of cases recognized and reported is not very large relative to the number of patients exposed, but we are very concerned that the long latency between initiation of treatment with Cylert and the first occurrence of signs of acute liver failure is so long that the link between treatment and failure may not be reliably made. If so, the actual incidence may be far greater than that reported.

Accordingly, we cannot agree to your proposal for labeling revisions and a Dear Dr. Letter. Instead, we ask that you adopt the labeling changes and text of the draft Dear Dr. letter that are attached to this letter. This labeling prominently warns of the risk of liver failure and identifies Cylert as a treatment that should only be considered for use among those failing to respond to alternative measures.

We are mindful that this decision imposes a severe restriction on the product's use, but given the risk, the nature of the condition being treated, and the availability of effective alternative marketed treatments, we have concluded our action constitutes the minimum intervention that can be justified.

In this regard, you should be aware that serious consideration was given to the option of asking that Cylert be withdrawn from marketing. We chose not to follow this course because we concluded that physicians and patients, if adequately informed about the nature and extent of the risk, should have the right to decide for themselves whether Cylert's benefits outweigh its risks in patients who fail to respond to alternative treatments.

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.

Your plans for the implementation of such a registry should be submitted to the NDA.

NDA 16-832  
NDA 17-703

NDA 16-832  
NDA 17-703

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If you have any questions, please contact Commander Steven D. Hardeman, R.Ph., Regulatory Management Officer at (301) 594-2777.

Sincerely yours. 

*/S/*

*9/14/96*

APPEARS THIS WAY

✓ Paul D. Leber, M.D.  
Director  
Division of Neuropharmacological  
Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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ON ORIGINAL

2

Page(s) Redacted

DRAFT  
DEAR DOCTOR  
LETTER

NDA 16-832  
NDA 17-703

cc:

Original NDAs 16-832, 17-703 /S/ 6-13-96

HFD-120/Div. Files

HFD-120/CSO/Hardeman

HFD-120/Leber/Laughren/Mosholder/Burkhart

HFD-733/Chen/Chamberlin/Graham

DISTRICT OFFICE

HFD-100/R Temple

HFD-2 / M. Longkin

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\cylertdd.13

Final: June 12, 1996

SUPPLEMENT REQUEST

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Nancy Chamberlin, Pharm.D.  
Reports Evaluation Branch, HFD-735

THROUGH: Robert T. O'Neill, Ph.D., Acting Director /S/ 4/17/96  
Division of Epidemiology and Surveillance, HFD-730

TO: Paul D. Leber, M.D., Division Director  
Division of Neuropharmacological Drugs, HFD-120

SUBJECT: Consult:  
Update on Cylert (pemoline) Associated Fatal Liver  
Failure

In response to your March 27, 1996 meeting request that liver failure reports associated with Cylert updated and liver failure reports for other drugs used for Attention Deficit Hyperactivity Disorder (ADHD) (Ritalin, and Dexedrine), and desipramine in children <19 years reviewed, we provide the following information, including clarification of counts of liver death cases, review of liver failure cases associated with Dexedrine and desipramine. Please refer to the previous Cylert MAR of February 8, 1996. Further comments on the Cylert and Ritalin risk assessment on liver failure will be provided by Dr. David Graham of Epidemiology Branch in a separate memo.

Reports of U.S. Liver Failure Cases

Counts of pediatric (<19 yrs) liver failure cases for Cylert, Ritalin, Dexedrine and desipramine are presented in the following Table 1. Further description of FDA counts in discrepancy with Abbott's will follow in the next section.

Table 1. Reports of U.S. Liver Failure Cases as of March 28, 1996 in children <19 years:

Drug Name	Deaths	Liver Transplants	L. Trans. Considered	Nonfatal Liver Failure	Total Liver Failure	Total All SRS Cases	Comments
Cylert	3	5	2	2	12	1284 (313*)	6 cases were not included in this count: M346786 Hx of biliary disease in a child, 2 foreign reports of deaths, and 3 U.S. reports in adults.
Abbott's	3	2	2	-	7		March 14, 1996 submission
Ritalin	0	1	0	1	2	2496 (94*)	1 case on a 32 yo IV abuser was not included; the 2 LF cases were potentially confounded and they will be reviewed by Dr. Graham.
Dexedrine	0	0	0	1	1	594 (9*)	This case was confounded (M1506772) as mentioned above under Ritalin.
Desipramine	1	0	0	0	1	2910 (77*)	Overdose liver necrosis in 19 YR M (M5026480)

\* Total number of reports in the SRS for all ages under the DES\_Liver (all liver related) COSTART term.

**BEST POSSIBLE COPY**

## Cylert

Abbott stated in their March 14, 1996 submission that they found 10 reports of liver death in patients <19 yrs: 3 foreign, 7 US (3 died, 2 **transplants**, 2 were considered for transplant). Due to their cut-off date for 1995, an additional new case of liver transplant received on February 29, 1996 was not included in their count but was provided in the March 14 submission.

As of March 26, 1996 the SRS and literature review identified 18 unduplicated reports of liver failure in all ages. Fifteen were categorized as liver death (outcome as death or had liver transplant) in which two were foreign pediatric reports of fulminant liver failure from Chile and Canada, and 3 were non-fatal. One case (#M346786) was excluded due to patient's history of biliary cirrhosis. Of the remaining 15 U.S. reports, there were 5 deaths (3 in patients <19 yrs, and 2 patients >19 years); 5 **transplants**; 2 considered for transplant; and 3 cases of non-fatal liver failure (2 pediatrics and 1 adults). Accordingly, the FDA has a total of 10 **U.S. liver deaths** in children <19 yrs.

### Discrepancy from Abbott's submission

Abbott's excluded case PCA #12878 was not located in the SRS and there were no specific details. Case #M346786 was excluded both by Abbott and us due to patient's history of biliary cirrhosis.

There were 2 reports from Michigan. One was in a 16 yo reported in 1988. The other was reported in a 11 yo published 4 years after the event by an Australian (M659770) which upon follow-up was the case occurring in Michigan in 1986. The latter case was excluded by Abbott counting it as a foreign case. However, Abbott counted another duplicate report on this 11 yo submitted by a reporter in Michigan (M386667). Therefore, the total number of cases from Michigan remains as two.

There were 3 **U.S. transplant** case reports that Abbott did not include in their counts. The possible reasons were:

1. One transplant case (PCA 69856) came in 1996 but was not included due to the 1995 cut-off date by Abbott.

2. Two transplant cases (M678873, M1566207) were excluded by Abbott, however, we could not exclude the possibility that pemoline contributed to the liver failure.

The following **Table 2** lists all liver failure cases (excluding one case of biliary cirrhosis) in the SRS. Bolded cases are the 10 U.S. liver death cases in <19 yo. Shadowed 3 cases are included in our counts but not in Abbott's.

APPEARS THIS WAY  
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SRS	#ABBOTT	AGE	SEX	LOCATION	OUTCOME
Fatal		Liver	Failure		
563032/ 569850	32488	16 YR	M	MI	DEATH (#1 US)
329404/ 127938	21085	12 YR	M	UNK	DEATH (#2 US)
NEW '93	65325	7 YR	F	TN	DEATH (#3 US)
1521412	NONE	79 YR	M	MASS	DEATH
74345	NONE	52 YR	F	CA	DEATH
1639681	93203	14 YR	M	CANADA	DEATH
NEW '95	96825	13 YR	M	CHILE	DEATH
Liver	Failure	Required	Liver	Trans-	plant
NEW' 96	69856	14 YR	F	NY	L TRANS (#4 US)
1416420	58731	11 YR	M	TN	L TRANS (#5 US)
1414590	59204	5 YR	M	TN	L TRANS (#6 US)
678873/ 646579	34179	11 YR	M	SC	L TRANS (#7 US)
1566207	61746	18 YR	M	NC	L TRANS (#8 US)
1570348/ 1621962	65163	7 YR	M	OH	L TRANS CONSIDERD (#9 US)
386667 659770	28268 82008B	11 YR	M	MI MI/AUST	L TRANS CONSIDERD (#10 US)
Non-Fatal	Liver	Failure			
416422	59089	40 YR	F	IA	NON-FATAL
333344 '84	25940	7 YR	M	KY	NON-FATAL LIVER BX- NECROSIS
333357 '84	26251	14 YR	M	NY	NON-FATAL LIVER BX- NECROSIS

## Ritalin

Dr. Graham will provide a review on 2 pediatric and one adult IV abuse liver failure cases under a separate memo.

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## Dexedrine

There are no liver-related adverse events listed in the labeling.

The SRS was searched on March 25, 1996 under Midlevel COSTART term DES\_LIVER for hepatotoxicity associated with the use of Dexedrine. Eight (7 unduplicated) reports were identified and reviewed. There were no deaths due to liver toxicity associated with Dexedrine. Five of the 7 reports had elevated liver enzymes. One case of hepatitis was reported in a 29-year-old female with the following concomitant medications: diphenylhydantoin (labeled for hepatitis & liver damage), reserpine and thyroid (M20973). However, the reporter indicated that the hepatitis was possibly secondary to the combined therapy.

Another case of liver failure/hepatitis/ascites was in a 9-year-old male which was difficult to make the assessment due to patient's prior use of Ritalin and Kwell overuse (14 days), and exposure to a salvage yard chemical spill (M1506772/ 1459251). This will be further discussed in Dr. Graham's review under Ritalin.

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## Desipramine

Desipramine is labeled in the Adverse Reactions section for *hepatitis, jaundice(simulating obstructive), altered liver function, elevated liver function tests, and elevated alkaline phosphatase* and in the Warnings section as *not recommended for use in children.*

The SRS was searched on March 27, 1996 under the Midlevel COSTART term DES\_LIVER for hepatotoxicity associated with the use of desipramine. Seventy-seven (73 unduplicated) cases were retrieved and reviewed and the breakdown of the serious events were: hepatitis-5, hepatomegaly-3, liver fatty-1, and necro liver-1.

Six reports were < 19 years in which one 19 yo male with prior history of suicide attempts (M5026480) died of overdose/liver necrosis. It did not provide any details. Although this case did not meet the case definition of liver failure according to Dr. Graham, it was included in Table 1.

The five remaining pediatric reports consisted of 4 of elevated liver enzymes and one of hepatitis/cholestat jaundice with concomitant Felbatol use (M1452714).

There were two other deaths in adults. One had fatty liver /convulsions/inc LDH in a 73 year old male on concomitant medications of Haldol, Hydrodiuril, Cogentin, Colace, viz(sic), Ativan Endep, Ascendin, Xanax, and resperine (M538339). The cause of death was listed as unknown/convulsion. The other one was in a 74 year old male who had elevated liver enzymes and with history of COPD and concomitant medications: Augmentin, Theodur, Zantac, Norpramine, Proventil inhaler, Atrovent Inhaler. The cause of death was unknown (M633389).

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List of All Drugs Associated with Liver Failure Reports in the SRS

For your information, the following was obtained from a search of the SRS for top 10 suspect drugs that had the most reported cases (unreviewed) of liver failure (in descending order):

acetaminophen (157)  
valproic acid (56)  
cyclosporine (54)  
diclofenac sodium (44)  
flutamide (37)  
interferon alfa-2b (28)  
phenytoin (28)  
ofloxacin (25)  
cilastatin sodium w/imipenem (24)  
rifampin (24)

The top 10 drugs that had the most reported **fatal** liver failure cases are (in descending order):

acetaminophen (103)  
cyclosporine (50)  
flutamide (30)  
valproic acid (30)  
diclofenac sodium (23)  
cilastatin sodium w/imipenem (22)  
ofloxacin (21)  
interferon alfa-2b (20)  
phenytoin (18)  
rifampin (18)

Summary

In response to Abbott's March 14, 1996 submission on fatal liver failure cases associated with Cylert, we provided counts of U.S. pediatric cases of liver failure associated with Cylert, Ritalin, Dexedrine and desipramine in this memo for your consideration. Abbott's liver death count (7) was 3 less than our count (10). Review of the liver failure cases associated with Dexedrine and desipramine revealed no similar patterns of liver toxicity to Cylert.

/S/

Nancy Chamberlin, Pharm.D

Concur:

                    /S/                    

Min Chen, M.S., R.Ph.  
Group Leader

                    /S/                    

David Barash, RPh.  
Branch Chief

- cc:  
HFD-120 Laughren/Mosholder  
HFD-730 O'Neill  
HFD-733 Graham / Davis  
HFD-735 Barash / Chen / Chamberlin  
HFD-735/ Chron / Consult file  
4-5-96nc  
rev:4-12-96nc

APR 12 1996  
FBI - MEMPHIS

APR 12 1996  
FBI - MEMPHIS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 17, 1996

FROM: Medical Officer, Epidemiology Branch (HFD-733)

THROUGH: Acting Director,  
Division of Pharmacovigilance and Epidemiology (HFD-730)

SUBJECT: Fulminant hepatic failure with pemoline (Cylert)

TO: Director,  
Division of Neuropharmacologic Drug Products (HFD-120)

RETURN

APR 24 1996

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/S/

This report updates our information and assessment of pemoline (Cylert) and liver failure, and responds to the sponsor's submission dated March 14, 1996.

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The sponsor's analysis differs from that presented in our report of February 2, 1996. Their analysis extended drug-usage data to 1995 compared to 1994 in our report; they included children up to age 19 compared to age 16 in our report; and they estimated that 40% of acute liver failure was of undetermined etiology compared with 11% in our report. The sponsor estimated a relative risk for acute liver failure of 4.1 compared to our estimate of 16.8, assuming no underreporting.

After reviewing the sponsor's submission, we conclude that they are in error, having substantially underestimated the background rate of fulminant hepatic failure (FHF), the condition described by the majority of cases reported to FDA with pemoline.

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Hepatic Failure

From a review of the subject, Lee reported about 2000 cases of acute liver failure occurred each year in the US.<sup>1</sup> Acute liver failure was defined as the onset of encephalopathy within six months of the onset of symptoms of liver disease. A small subset of this group was labeled as FHF, in which the time course from jaundice to encephalopathy is eight weeks or less.<sup>1</sup>

With a US population of about 250,000,000, the occurrence of 2,000 cases per year would translate to an incidence rate for acute liver failure of about 8 per million per year. From data published by the United Network for Organ Sharing (UNOS), less than 11% of liver transplants in children were for situations involving a fulminant presentation.<sup>2</sup> Among cases with a fulminant presentation, about half (5.8% of all transplants) had an unspecified or undetermined etiology. This would yield an estimate for the incidence rate of FHF in children of less than 0.5 per million per year.

Based on these data, we believe that the population-based rate for FHF due to unknown/unspecified etiology is below 0.5 per million in the age group of primary interest in this analysis (table 1).

Table 1. Liver transplants in children by age in the US, 1993

	0-5	6-15	0-15
Liver transplants (#)	279	128	407
US population (x 10 <sup>6</sup> )	16.0	43.9	59.9
Transplant rate (x 10 <sup>-6</sup> )	17.4	2.9	6.8
Fulminant, unspecified			0.55

Although we do not have data on the proportion of liver transplants performed in the setting of fulminant disease in children broken down by age-group, the substantially lower overall transplant rate in older children compared to younger children (2.9 per million vs 17.4 per million) provides strong evidence that the rate for fulminant disease is below 0.5 per million.

The sponsor's rate estimate for FHF of about 4 per million is clearly too high.

#### Cases of liver failure

Table 2 (see end of report) summarizes details from 19 cases of major liver injury or failure reported to FDA with pemoline. The first 11 cases are of liver failure in US children below age 20. Eight definitely meet the definition of FHF; cases #5 and #8 also appear to meet the definition but additional follow-up is being pursued; we are unable to follow-up on the 1977 case (#1) due to incomplete information. This case also could represent fulminant disease.

The next three cases represent more prolonged/chronic disease in US children treated with pemoline. Case 12 presented with hepatomegaly and transaminase elevations of 3-6 times normal which persisted over months after pemoline was stopped. Liver biopsy showed bridging necrosis and portal fibrosis. Over the subsequent five months, liver size and transaminase levels normalized. Case 13 had persistent mild transaminase elevations over many months. A liver biopsy was read as showing chronic active hepatitis. Case 14 stopped pemoline use when low grade transaminase elevations were noted on routine bloodwork. Persistent transaminits led to liver biopsy five months later which showed "cryptogenic cirrhosis". The process continued and liver transplantation was performed about five months after this.

There were three cases of severe liver disease reported in US adults treated with pemoline. Case 15 died of liver failure after a three week course, bearing close resemblance to cases of fulminant disease in children. Case 16 involved an elderly man treated with pemoline for sleep apnea who developed hepatitis with coagulopathy and was hospitalized. Altered mental status was reported to have been intermittently present, but review of hospital records suggest that hepatic encephalopathy was not present. The patient developed hepatorenal syndrome and died. Case 17 had a similar presentation with hepatitis and coagulopathy. We do not know if encephalopathy developed.

Finally, two additional cases of FHF in children were reported to FDA from foreign sources.

#### Fulminant hepatic failure

Of the 14 cases of liver failure in children, one (#13) was chronic in onset. The remaining 13 appear to have been acute, most or all being fulminant in onset and progression. Among these, 11 were male. The median age was 12 years. The median duration of pemoline use was 13 months. The median time course of disease progression from jaundice to encephalopathy, transplant or death was 2 weeks. Dose was reported in seven cases with a median of 65.625 mg. There were six deaths of which two occurred while awaiting liver transplant and two others followed transplant. Seven patients underwent liver transplantation.

Using drug-use data provided by the sponsor in their submission, there were nearly 7.2 million prescriptions for pemoline over the years 1975-1995. From other IMS data, each prescription represented about one month of person-time of use, for a total of 597,000 person-years. Seventy-two percent of use was in children

of age, representing about 430,000 person-years of exposure risk. With 8 cases, the reporting rate would be 18.6 per million person-years; with 11 cases, 25.6 per million person-years.

### Relative risk of fulminant hepatic failure

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Given a background rate for FHF in children of less than 0.5 per million person-years, the relative risk estimate for pemoline use This, is based on 8-11 US case reports.

Underreporting is a major limitation of spontaneous reporting systems. In most settings where the level of reporting has been quantitated, reporting efficiency for hospitalized or fatal adverse events has been found To the extent that cases of FHF with pemoline use have been underreported to FDA, the incidence rate and relative risk have also been correspondingly underestimated. If 50% of cases have been reported, representing an extraordinarily high reporting efficiency, relative risk estimates would double to If 10% of cases have been reported, the relative risk estimates would increase 10-fold over that shown above.

### Absolute risk of fulminant hepatic failure

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From literature on the treatment and natural history of attention deficit disorder (ADD), the average duration of drug treatment is about 2.5 years.<sup>6-7</sup> Among 430,000 person-years of pemoline use, this would translate to about 172,000 individuals aged years. With 8-11 reported cases of fulminant disease, the absolute risk ranges from With a reporting efficiency of 50%, absolute risk would range from If 10% of cases have been reported, absolute risk would be about 1 per 2,000.

### Discussion

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Fulminant hepatic failure is a small subset of the category of acute liver failure. It carries a mortality rate of in the absence of liver transplantation.<sup>1,8</sup> The hallmark of this disorder is its rapid progression from onset of jaundice to encephalopathy within 8 weeks or less.

FDA has received 10-13 cases of fulminant disease in children treated with pemoline. Using data on acute liver failure, liver transplantation and US population figures, we estimated the relative risk of FHF to be in US children treated with pemoline. If underreporting of this reaction is comparable to that found in the literature, the true relative risk may be as high as

The median duration of pemoline use prior to symptomatic liver disease was about 13 months, with the shortest duration among our cases of 6 months. Ten of 13 cases had durations of prior use of 12 months or greater. One might argue that the first 6-12 months of pemoline use carry lower risk than longer term use. If this is so, and the hazard function rises steeply beyond some time point, then the relative and absolute risks also would rise beyond that time point. The estimates presented above can be viewed as a composite of lower risk during the initial time period coupled with higher risk during the latter time period. Because we lack data on the frequency distribution of pemoline users by duration of use, we are unable to estimate the impact of a changing hazard rate on either the relative or absolute risk. The effect on absolute risk could be great.

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The greatest difference between our analysis and that of the sponsor relates to the estimation of the background rate of FHF in children. The sponsor's approach appears to have failed to distinguish between acute and fulminant failure. According to UNOS data, about 11% of transplants are in settings of fulminant disease.<sup>2</sup> From this, we might expect about a 9-fold lower incidence rate for fulminant disease. The sponsor's estimated rate was about 4 per million compared with our estimate of less than 0.5 per million, closely mirroring the expected difference between acute and FHF.

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The sponsor's approach to estimation of the number of individuals ever treated with pemoline over the marketing history of the drug is seriously flawed. The sponsor took exposure prevalence data from a one year period (1993-94) in three health care plans and made the assumption that this accurately reflected the prior 20 years or so of pemoline use. This is clearly not accurate. From National Prescription Audit data for pemoline from 1975-1995, there has been a rapid growth in pemoline prescriptions most especially in the past three years. In this time, annual prescription totals have increased almost 100%. In other words, prevalence estimates today are about double what they were four years ago. The sponsor's approach has seriously overestimated prevalence of pemoline use over its marketing lifetime, and hence has overestimated the total number of patients ever treated with the drug. Consequently, the sponsor's estimation of absolute risk is much lower than the true value.

Our approach to estimation of absolute risk relied on survey data for the treatment of attention deficit disorder.<sup>6,7</sup> This approach took account of age-specific variations in ADD treatment duration. As such, we believe it provides a reasonable mean estimate of the number of patients ever treated with pemoline. A major problem is that we do not know the proportional distribution of pemoline users by duration of use. It is possible that more than 172,000 people

have ever been exposed to pemoline, but that the number remaining on treatment for 6 months or longer is smaller. It is at about 6 months of use that our earliest case occurred. Depending on drop-off of use with longer durations, it is possible that the absolute risk (and the relative risk) increase substantially.

As detailed in our previous report, underreporting of cases is an important consideration. Previous studies have found that serious or fatal adverse events are reported about 10% of the time.<sup>3-5</sup> To the extent that pemoline cases have been underreported, the estimates of relative and absolute risk would need to be proportionately increased.

### Conclusion

The sponsor's approach has seriously underestimated the true relative and absolute risk of fulminant hepatic failure associated with pemoline use.

Because of underreporting, there could easily be as many cases of FHF with pemoline as have been reported thus far. This would increase substantially all estimates of the relative and absolute risk.

Data describing the pattern of pemoline use duration are needed to better quantitate the absolute risk, especially among patients who remain on the product beyond 6 or 12 months.

/S/

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Table 2. Cases of severe liver disease with pemoline reported to FDA

<u>Year</u>	<u>source</u>	<u>Age</u>	<u>Sex</u>	<u>Use in Months</u>	<u>Time Course</u>	<u>Encephalopathy</u>	<u>Coagulopathy</u>	<u>Biopsy</u>	<u>Transplant</u>	<u>Outcome</u>	<u>Dose in mg</u>
1. 1977		11	M	12						Died	
2. 1981	NJ	12	M	9	1 wk	+	+	+		Died	56.25
3. 1986	MI	11	M	66	4 wk	+	+	+	*	Alive	37.5
4. 1988	MI	16	M	18	1 wk	+			**	Died	
5. 1991	TN	15	M	36	?1 wk			+	+	Alive	112.5
6. 1992	TN	11	M	12	4 wk	+		+	+	Alive	
7. 1993	TN	5	M	12	4 wk	+	+	+	+	Alive	
8. 1993	TN	7	F	13	1 wk	+		+	**	Died	37.5
9. 1994	NC	16	M	18+	?4 wk				+	Alive	75
10. 1995	OH	7	M	10	2 wk	+			*	Alive	
11. 1996	NY	14	F	6	2 wk	+			+	Alive	112.5
12. 1984	KY	7	M							Alive	
13. 1984	NY	14	M					+		Alive	
14. 1989	SC	11	M	32	Long			+	+	Alive	37.5
15. 1975	CA	52	F		3 wk					Died	
16. 1994	MA	79	M	6			+	+		Died	
17. 1994	IA	40	F	84			+			Alive	
18. 1993	CAN	14	M	15	3 wk	+	+	+	+	Died	37.5
19. 1995	CHL	13	M	22	1 wk	+			+	Died	75

\* Transplant under consideration  
 \*\* Died awaiting transplant

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