CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 16832/S013

Trade Name: CYLERT TABLETS

Generic Name: PEMOLINE

Sponsor: ABBOTT LABORATORIES

Approval Date: 4/11/98

Indication(s): TREATMENT OF ATTENTION DEFICIT DISORDER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 16832/S013

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Medical Review(s)				X
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EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 16832/S013

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

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,

/S/

4/8/96

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 /S/ 4-5-96
HFD-120/Div. files
HFD-120/CSO/S.Hardeman /S/ 4/4/96
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.)

Final: April 4, 1996

c:\docs\nda\cylert\change1.fpl

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 16832/S013

FINAL PRINTED LABELING

Labeling: SLR-013

NDA No: 16-832 Rc'd. 7-11-96

Reviewed by: /S/

APPROVED
APR 11 1996

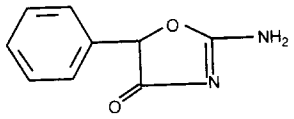
(Nos. 6025, 6057, 6073, and 6088)
03-4633-R17-Rev. December, 1995

CYLERT®
(PEMOLINE)

DESCRIPTION

CYLERT (pemoline) is a central nervous system stimulant. Pemoline is structurally dissimilar to the amphetamines and methylphenidate.

It is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazolin-4-one. Pemoline has the following structural formula:



Pemoline is a white, tasteless, odorless powder, relatively insoluble (less than 1 mg/mL) in water, chloroform, ether, acetone, and benzene; its solubility in 95% ethyl alcohol is 2.2 mg/mL.

CYLERT (pemoline) is supplied as tablets containing 18.75 mg, 37.5 mg or 75 mg of pemoline for oral administration. CYLERT is also available as chewable tablets containing 37.5 mg of pemoline.

Inactive Ingredients

18.75 mg tablet: corn starch, gelatin, lactose, magnesium hydroxide, polyethylene glycol and talc.

37.5 mg tablet: corn starch, FD&C Yellow No. 6, gelatin, lactose, magnesium hydroxide, polyethylene glycol and talc.

37.5 mg chewable tablet: corn starch, FD&C Yellow No. 6, magnesium hydroxide, magnesium stearate, mannitol, polyethylene glycol, povidone, talc and artificial flavor.

75 mg tablet: corn starch, gelatin, iron oxide, lactose, magnesium hydroxide, polyethylene glycol and talc.

CLINICAL PHARMACOLOGY

CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Pemoline is rapidly absorbed from the gastrointestinal tract. Approximately 50% is bound to plasma proteins. The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days. In animals given radiolabeled pemoline, the drug was widely and uniformly distributed throughout the tissues, including the brain.

Pemoline is metabolized by the liver. Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys with approximately 50% excreted unchanged and only minor fractions present as metabolites.

CYLERT (pemoline) has a gradual onset of [illegible] recommended schedule of

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS AND USAGE

CYLERT (pemoline) is indicated in Attention Deficit Disorder (ADD) with hyperactivity as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

CONTRAINDICATIONS

CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. CYLERT should not be administered to patients with impaired hepatic function (see **ADVERSE REACTIONS**).

WARNINGS

Decrements in the predicted growth (i.e., weight gain and/or height) rate have been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

PRECAUTIONS

General:
Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

CYLERT should be administered with caution to patients with significantly impaired renal function.

Laboratory Tests:
Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See **ADVERSE REACTIONS** regarding reports of abnormal liver function tests, hepatitis and jaundice.)

Drug Interactions:
The interaction of CYLERT (pemoline) with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

Decreased seizure threshold has been reported in patients receiving CYLERT concomitantly with *antiepileptic medications*.

Carcinogenesis:
Long-term studies have been conducted in rats with doses as high as 150 mg/kg/day for eighteen months. There was no significant difference in the incidence of any neoplasm between treated and control animals.

Mutagenesis:
Data are not available concerning long-term effects on mutagenicity in animals or humans.

Impairment of Fertility:
The results of studies in which rats were given 18.75 and 37.5 mg/kg/day indicated that pemoline did not affect fertility in males or females at those doses.

Pregnancy:
Teratogenic effects: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses of 18.75 and 37.5 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic effects:
Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg/kg/day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg/kg/day.

(OVER)

Labeling: SLR-013
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APPROVED
APR 11 1996

Nursing Mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CYLERT is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness in children below the age of 6 years have not been established.

Long-term effects of CYLERT in children have not been established (see **WARNINGS**).

CNS stimulants, including pemoline, have been reported to precipitate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Drug treatment is not indicated in all cases of ADD with hyperactivity and should be considered only in light of complete history and evaluation of the child. The decision to prescribe CYLERT (pemoline) should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

ADVERSE REACTIONS

The following are adverse reactions in decreasing order of severity within each category associated with CYLERT:

Hepatic: There have been reports of hepatic dysfunction including elevated liver enzymes, hepatitis and jaundice in patients taking CYLERT. The occurrence of elevated liver enzymes is not rare and these reactions appear to be reversible upon drug discontinuance. Most patients with elevated liver enzymes were asymptomatic. Although no causal relationship has been established, there have been rare reports of hepatic-related fatalities involving patients taking CYLERT.

Hematopoietic: There have been isolated reports of aplastic anemia.

Central Nervous System: The following CNS effects have been reported with the use of CYLERT: convulsive seizures; literature reports indicate that CYLERT may precipitate attacks of Gilles de la Tourette syndrome; hallucinations; dyskinetic movements of the tongue, lips, face and extremities; abnormal oculomotor function including nystagmus and oculogyric crisis; mild depression; dizziness; increased irritability; headache; and drowsiness.

Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Gastrointestinal: Anorexia and weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Nausea and stomach ache have also been reported.

Genitourinary: A case of elevated acid phosphatase in association with prostatic enlargement has been reported in a 63 year old male who was treated with CYLERT for sleepiness. The acid phosphatase normalized with discontinuation of CYLERT and was again elevated with rechallenge.

Miscellaneous: Suppression of growth has been reported with the long-term use of stimulants in children. (See **WARNINGS**.) Skin rash has been reported with CYLERT.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: CYLERT is subject to control under DEA schedule IV.

Abuse: CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

OVERDOSAGE

Signs and symptoms of acute overdosage, [illegible] from overstimulation of the

Labeling: SAR-01
NDA No: 16-832
Reviewed by: ____

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, 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 reported in the literature to be useful in decreasing CNS stimulation and sympathomimetic effects.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for CYLERT overdosage has not been established.

DOSAGE AND ADMINISTRATION

CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg/day. This daily dose should be gradually increased by 18.75 mg at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

HOW SUPPLIED

CYLERT (pemoline) is supplied as monogrammed, grooved tablets in three dosage strengths:

18.75 mg tablets (white) in bottles of 100 (**NDC** 0074-6025-13);

37.5 mg tablets (orange-colored) in bottles of 100 (**NDC** 0074-6057-13);

75 mg tablets (tan-colored) in bottles of 100 (**NDC** 0074-6073-13).

CYLERT (pemoline) Chewable is supplied as 37.5 mg monogrammed, grooved tablets (orange-colored) in bottles of 100 (**NDC** 0074-6088-13).

Recommended Storage: Store below 86°F (30°C).

ABBOTT LABORATORIES
NORTH CHICAGO, IL60064, U.S.A.
PRINTED IN U.S.A.

CYLERT® (PEMOLINE)

(Nos. 6025, 6057, 6073, and 6088)
03-4633-R17-Rev. December, 1995

034633

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 16832/S013

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

TECH

NDA NO. 16-832 REF. NO. SLR-013

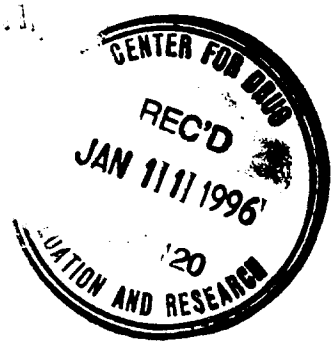
NDA SUPPL FOR Labeling

ABBOTT

Pharmaceutical Products Division

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

January 5, 1996



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

Re: Cylert ® Tablets (pemoline)
NDA 16-832

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 the draft package insert 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.

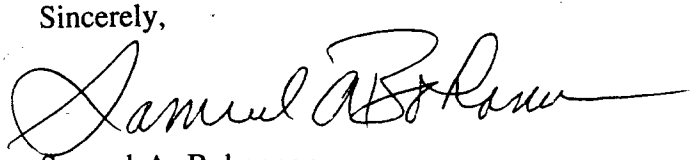
Regarding Chemistry, manufacture, and controls, the labeling is satisfactory.

/S/

4/3/96

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:tll
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

JUN 14 1996

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

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.

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

Sincerely yours,

/S/ 9/17/96

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

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 /S/ 6/12/96 /S/ 6/12/96
HFD-120/Leber/Laughren/Mosholder/Burkhart
HFD-733/Chen/Chamberlin/Graham
DISTRICT OFFICE
HFD-100/RTemple
HFD-2/M.Laughren
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Final: June 12, 1996

SUPPLEMENT REQUEST

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 Trans-plants	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.

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.

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.

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.

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).

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

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

RETURN

DATE: April 17, 1996

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

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

SUBJECT: Fulminant hepatic failure with pemoline (Cylert)

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

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

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.

Hepatic Failure

From a review of the subject, Lee reported about 2000 cases of acute liver failure occurred each year in the US.[1] 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.[1]

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.[2] 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 10^6)	16.0	43.9	59.9
Transplant rate (x 10^{-6})	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

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

From literature on the treatment and natural history of attention deficit disorder (ADD), the average duration of drug treatment is about 2.5 years.[6-7] 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

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.[1,8] 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.

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.[2] 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.

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.[6,7] 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.[3-5] 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/

David J. Graham, MD, MPH

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

	Year	Source	Age	Sex	Use in Months	Time Course	Encephalopathy	Coagulopathy	Biopsy	Transplant	Outcome	Dose in mg
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.		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