CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 16832/S014

Trade Name: CYLERT TABLETS

Generic Name: PEMOLINE

Sponsor: ABBOTT LABORATORIES

Approval Date: 9/9/96

Indication(s): TREATMENT OF ATTENTION DEFICIT DISORDER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 16832/S014

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	Included	Pending Completion	Not Prepared	Not Required
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Chemistry Review(s)	X			
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
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 16832/S014

APPROVAL LETTER

SEP 9 1996

NDA 16-832/S-014

Abbott Laboratories
Attn: Samuel A. Bohannon
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

Dear Mr Bohannon:

We acknowledge receipt on April 12, 1996 of your supplemental New Drug Application (NDA) dated April 11, 1996 submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Cylert® (Pemoline) Tablets, 18.75, 37.5, and 75 mg.

The supplemental application provides for a change in the assay methodology

We have completed the review of this supplemental application and it is approved.

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

Sincerely yours,

/S/

Stanley W. Blum, Ph.D.,
Chemistry Team Leader, DNDC I
Division of Neuropharmacological Drug Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Original NDA 16-832/SCS-014
Div. File HFD-120/
/WBrannon/S/ 9/4/96
/CSO/SHardeman/
Supv. Init. /SBlum/
HFD-80/
HFR-MW100/CHI-DO/
n:\brannon\16832014.let

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 16832/S014

CHEMISTRY REVIEW(S)

SEP _ 4 1996

CHEMISTS REVIEW OF SUPPLEMENT

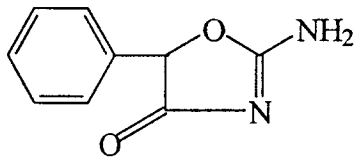
1. ORGANIZATION: HFD-120
2. NDA NUMBER: 16-832
4. SUPPLEMENT NUMBERS/DATES: SCS-014
LETTERDATE 11-APR-96
STAMPDATE 12-APR-96
5. AMENDMENTS/REPORTS/DATES:
LETTERDATE
STAMPDATE
6. REC'D BY CHM: 12-APR-96

7. APPLICANT NAME AND ADDRESS:

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

8. NAME OF DRUG: **Cylert**
9. NONPROPRIETARY NAME: Pemoline
10. CHEMICAL NAME/STRUCTURE:
4(5H)-Oxazolone, 2-amino-5-phenyl-

$C_9H_8N_2O_2$



Mol Wt. 176.18

CAS registry # 2152-34-3
11. DOSAGE FORM(S): Tablets
12. POTENCY(IES): 18.75 mg, 37.5 mg, and 75 mg
13. PHARM. CATEGORY:
14. HOW DISPENSED:
15. RECORDS AND REPORTSCURRENT:
16. RELATED IND/NDA/DMF(S):
17. SUPPLEMENT PROVIDES FOR: a change in the assay methodology for a component used in the
18. COMMENTS

19. CONCLUSIONS AND RECOMMENDATIONS: Issue an approval letter.

20. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Wilson Brannon	/S/	29-AUG-96

Copies:
ORIG; NDA NUMBER 16-832/SCS-014
HFD-120
HFD-120/CSO/SHardeman/
HFD-120/WBrannon/
filename: n:\brannon\16832014.sup
INIT: SW BLUM /S/

8/30/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 16832/S014

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

ABBOTT

ORIGINAL

NDA NO. 16-832 REF. NO. SCS-014

NDA SUPPL FOR Controls

Pharmaceutical Products Division

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

NDA SUPPLEMENT

April 11, 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
NDA 16-832

Special Supplement
Changes Being Effected

Dear Dr. Leber:

Pursuant to 21 CFR 314.70 (c), Abbott Laboratories submits this supplement to change the assay methodology for

These above mentioned data were discussed with Dr. Stanley Blum, Supervisory Chemist, Division of Neuropharmacological Drug Products, in a telephone conversation on January 15, 1996. Dr. Blum stated that Abbott should file a Changes Being Effected Supplement with the above data plus data on at least three lots comparing the current method to the new method.

The above referenced experimental data is in the enclosed validation report. In addition, the validation report contains a table (page 4, Table 3) which presents a comparison of data on six lots of

The following information is provided behind the tabs to support this change:

Please contact me at the telephone number noted below if there are any questions concerning this submission.

Sincerely,

Samuel A. Bohannon
Product Manager, PPD Regulatory Affairs
D-491, AP6B-1, (847) 937-0859
Fax: (847) 937-8002

SAB:tll

Copy of Correspondence to:

Stanley Blum, Ph.D., Supervisory Chemistry Reviewer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

MEMORANDUM

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

DATE: September 19, 1996

FROM: Greg Burkhart,
Safety Team Leader, Neuropharmacological Drug Products, HFD-120

TO: Paul Leber,
Director, Division of Neuropharmacological Drug Products, HFD-120

&

Tom Laughren
Team Leader, Psychiatric Drug Products, HFD-120

SUBJECT: Review of General Correspondence: Abbott Response to 6/14/96 FDA Letter on Acute Hepatic Failure and Cylert.

In general correspondence, dated 8/01/96, Abbott outlined their disagreement with the Epidemiology Branch (EB) analysis and interpretation of the 10 reported cases of acute hepatic failure (AHF) in Cylert users aged In short, Abbott concedes that the number of reported cases significantly exceeds that expected and that Cylert labeling should be revised to convey, in a boxed warning, that the risk of AHF is increased with Cylert use.

The major point of disagreement is the absolute risk (AR) estimate, and in particular, the number of Cylert users who were aged for use in the denominator of that estimate. While strong disagreement exists about the most valid background rate to use to estimate the relative risk (RR), the disagreement has little regulatory significance since all parties interpret the Cylert AHF reporting rate as a "strong signal" of risk that is probably attributable to Cylert use. The correspondence also provides a discussion by Dr. Strom who was engaged by Abbott, contrasting the value of a formal patient registry with that of a non-randomized retrospective study.

This memorandum will first focus on the epidemiological issues that are being debated and then consider Dr. Strom's points.

Epidemiologic Issues Regarding the Hepatotoxicitiy Signal

Estimating the Absolute Number of Cylert Users

The major point of disagreement between the EB and Abbott is the estimated number of patients who have ever used Cylert. In the 6/14/96 FDA letter, HFD-120 proposed language in the boxed warning stating that "1 in 15,000 Cylert treated patients aged five to 19 will develop life threatening liver failure". This risk estimate, which was provided by the EB (actually the EB's estimate was 1 in 15,600), was based upon three sources of data for its derivation: (1) IMS's National Prescriptions Audit (NPA); (2) IMS's National Disease and Therapeutic Index (NDTI), and (3) survey data from Baltimore school children (Safer Survey[1]).

Abbott and the EB agreed that the NPA database provided a starting point to estimate the person-time at risk for Cylert use. The NPA uses a sample of slightly over 30,000 US non-institutional pharmacies that are purported to be a representative sample. The NPA has generally been accepted as the best means to estimate the extent of use for a given drug product and its estimates compare favorably well with other estimates of drug use when they exist. According to IMS, an NPA estimate projects to about 85% of US use.[2]

One problem with the NPA database is that data on the demographic characteristics of the patients are not collected. Thus, to estimate the extent of use of a product for a specific age range other sources of data external to the NPA database are necessary. Age-specific use can be derived from databases such as state Medicaid programs, HMO prescription claims databases or IMS's NDTI database with the latter database used by the EB in this case. NDTI is comprised of clinical data collected by about 3000 office based physicians who voluntarily record aspects of their interactions with patients 2 days a month. The data recorded includes recommended prescription drug treatments and demographic characteristics of the patients. While formal evaluation of the generalizability of the these data have not been performed, I have been dubious of NDTI's value given that there are about 650,000 practicing US physicians and the absolute number of mentions for most drug products are relatively small.

In the NDTI database, about 72% of Cylert mentions were for patients aged The EB and Abbott applied this estimate to the estimated number of Cylert prescriptions from NPA to estimate the number of prescriptions in . Person-time at risk was then estimated by assuming that each prescription provided 30 days of use. Both Abbott and the EB used this estimate as the basis for calculating the reporting rate in Cylert users agec There is no disagreement that this rate significantly exceeds that expected.

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1 The JAMA article (1988;260:2256-8.) summarizes the trend observed from 9 biannual surveys.
2 I usually divide the NPA estimate by 0.85 to further project to the US since the opportunity to report an event is usually not restricted.

One problem with evaluating signals derived from spontaneous reporting has always been how to convey the public health significance of the suspected increase in risk. While RR is useful for qualifying the strength of signal, and therefore to argue causality, RR by itself it is not useful for making risk benefit decisions. The AR, and more specifically, the attributable risk quantifies the public health impact from any the resulting disease caused by any putative exposure.

To estimate the AR of AHF during Cylert use, the EB used the published data from the Safer surveys on the average length of drug treatment for ADHD. The person-years of Cylert use were divided by this average length of use to derive the estimated number of Cylert users with the AR of AHF in Cylert users calculated by dividing the number of reported cases into that estimate.

In Abbott's opinion, the use of the Safer data resulted in a "gross underestimate" of the denominator and hence, and overestimate of the AR. In Abbott's review of the publications describing the Safer surveys, several flaws were noted. In my read of the JAMA article there are several issues that would limit the generalizability of that data. First, the length of use cited is not drug specific. Second, the documentation in the JAMA article is difficult to follow, not providing clear documentation of the methods or any supporting data. The article simply states that the average duration of ADHD medication use was 2 years in elementary school, 4 years in middle school and 7 years in senior high school.[3] Safer also noted that Baltimore has an increased prevalence of treated ADHD.

Upon receiving the Abbott 8/01/96 response, we requested a response from the EB to the Abbott criticisms. Although a written response has not been received, I discussed the issue with Dr. Graham. Apparently, the EB is currently trying to estimate the hazard of Cylert discontinuation from several claims databases, again trying to apply that estimate to the person-time at risk to estimate the number of Cylert users. The EB has been conducting a cohort study of AHF in Cylert users in Medicaid having identified 2 possible cases. However they are still waiting on medical records to confirm that these patients had AHF from an unknown cause. In my opinion, both efforts are unlikely to provide precise enough point estimates of the AR of AHF in Cylert users to use in labeling.

Abbott also attempted to estimate the AR using the average yearly reporting rate for 1990-1995 during which Abbott feels the use data are most reliable. This method also is of uncertain value and probably imprecise.

Thus, without even considering the difficulties in estimating the AR, there is significant uncertainty at (1) estimating the number of Cylert prescriptions in year old patients (2) estimating the person-time at risk and (3) quantifying the extent of under-reporting. Adding further complexity is the difficulty is reliably estimating the AR. Such uncertainty exists even without considering the wide confidence limits that may obtain for any valid estimate. Thus, my

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3 I am not sure where the 2.5 year estimate came from - perhaps the other references cited by Dr. Graham.

conclusion is that there is wide range of point estimates that are consistent with the current experience; at one end, high enough to warrant major concern while at the other end, low enough to merit mention but not necessarily alarming.

Updated Reporting Rates for Acute Hepatic Failure

In Abbott's response, they point out that one case of AHF counted by the EB was a duplicate report for a previously counted case. Summarizing the case counts and use through May 1996 in 5-19 year olds, there have been 10 domestic cases of AHF reported to the FDA for estimated 460,800 person-years of Cylert use. The AHF reporting rate is about 1 per 50,000 person-years of Cylert use. Using a background rate of 1 per million person-years gives a RR estimate of 20.

Estimating the Background Rates for AHF

For the US population aged 5-19, the EB used a background rate of 0.5 per million person-years while Abbott used 4 per million person-years as the background rate. As implied earlier, using either background rate results in a significantly increased relative risk of AHF with Cylert with both estimates interpreted as a strong signal of risk.

Abbott's background rate estimate is based upon a literature based assumption that the background rate is 1 per 100,000 for all causes of AHF and that 40% of the cases are due to unknown causes. The EB is based upon liver transplantation data similar to the published data that I have previously used for such estimates. In 1993, there were 33 transplants in patients aged 0-19 that were for fulminant liver failure of an unspecified cause with the US population was estimated at 74,008,000 for this age group in 1993. Based upon the clinical literature, I assumed that about 50% of fulminant liver failure cases die before making it to transplant. This would give about 66 cases or about 1 per million person-years. Although all these estimates are likely imprecise, Abbott's estimate is less appealing because they have used the experience from all ages combined in spite of data suggesting that the background rate, of even AHF of an unknown cause, increases with age.

The Value of a Registry Contrasted with That of a Formal Non-Randomized Study

Dr. Strom provides a discussion of the value of a registry contrasted with that of a retrospective cohort study that could be conducted in a linked health claim database. While he makes several good points regarding the value of a formal study, he minimizes the difficulty of a retrospective study of AHF that would have to be based upon medical record review. Since we are interested in cases that clearly do not have another possible cause such as from viral hepatitis, most hospital records for admissions related to any liver dysfunction will have to be reviewed. Such review will be expensive and may not necessarily be judged successful depending on record retrieval rates and the adequacy of the clinical data. A case-control study conducted in UNOS would seem to be better comparative retrospective design.

Dr. Strom also points out the limitations of a formal registry, which are substantial, but minimizes the value of prospective data collection for this issue. Considering how difficult it may be to implement a registry of all Cylert users, perhaps the discussion should focus on the value of a prospective cohort study. Such a study could collect data on all liver outcomes with the primary objective being to set an upper limit on the risk of AHF. For example, if 5000 new users could be enrolled and followed for at least 6 months and no AHF cases are observed, this finding would be quite informative regarding the expected level of AR. Alternatively, if only one or two cases are observed in these 5000 Cylert users, enrollment could continue. While Dr. Strom is correct that a control group would also be informative, as would randomization of treatment, it may be difficult to define an appropriate comparison drug.

Recommendations

1) Given the uncertainty of the AR estimate, a range of estimates could be described in the labeling or it may be better to leave discussion of AR out of the label. My preference is the latter. Including a statement that mentioned the reporting rate would also seem to be of little value since we have no way to quantify the extent of under-reporting. A short description of the cases and why we think this is a signal - that the reporting rate is many fold greater than either that for methylphenidate or the background rate in the general population, may be helpful.

2) The warning statement in the 6/14/96 FDA letter seems better articulated than Abbott's proposed wording.

3) The sponsor could conduct a prospective single cohort study of Cylert users with a minimum enrollment of 5000 users followed for 6 months. Clinical data collection could occur - concurrent with event occurrence limiting the need to collect clinical data on all cohort members If any cases of unexplained AHF are observed, enrollment could be continued. Follow-up should focus on all hepatic outcomes and Abbott should provide biannual study updates.

4) If there is concern that all ADHD patients carry a higher background risk for unexplained AHF, but the reporting to the FDA has been greater for Cylert creating the signal, then a retrospective study, perhaps conducted in UNOS, could also be considered. However, if Cylert users have an increased background rate beyond that of ADHD patients because of patient selection factors, then randomization of treatment would be necessary, and if feasible, could be applied to the prospective cohort study noted above.

/S/ 9-19-96

Greg Burkhart, M.D., M.S.
Safety Team Leader
Neuropharmacological Drug Products

cc:HFD-120\Burkhart\Hardeman\Mosholder\NDA nos. 16-832, 17-703

NDA 16-832
NDA 17-703

JUN 28 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 submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Cylert (pemoline) Tablets and Chewable Tablets.

We also refer to the telephone conversation of June 18, 1996, between Dr. Steven I. Engel of your firm and Mr. Steven D. Hardeman of this Division, in which Dr. Engel requested a copy of the analyses prepared to support the Division's letter of June 14, 1996.

As requested, a copy of the Division of Pharmacovigilance and Epidemiology review, prepared by Dr. David Graham, is enclosed.

Should you have any questions, please contact:

Commander Steven D. Hardeman, R.Ph.
Senior Regulatory Management Officer
Telephone: (301) 594-5533

Sincerely yours,

/S/

6/26/96

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

enclosed documents:
M.O. Review

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDAs 16-832, 17-703
HFD-120/Div. Files
HFD-120/CSO/Hardeman 6/25/96 /S/
HFD-120/Leber/Laughren/Mosholder
/S/ 6-26-96

c:\docs\nda\cylert\cylert.l4

final: June 25, 1996

GENERAL CORRESPONDENCE (GC)

MEMORANDUM

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

DATE: October 11, 1996

FROM: Greg Burkhart,
Safety Team Leader, Neuropharmacological Drug Products, HFD-120

TO: Paul Leber,
Director, Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Recommendation for changes in Cylert labeling to reflect the risk for acute hepatic failure.

Recommendation

Given that the number of reported cases of acute hepatic failure (AHF) in Cylert users exceeds all estimates of the number expected even without considering under-reporting, changes in Cylert labeling are proposed that reflect the likely association between Cylert use and AHF.

The *Indication* section has been modified to state that Cylert should not ordinarily be considered as first line drug therapy. In addition, changes have been made to the *Warnings*, *Precautions* and *Adverse Reactions* sections of the labeling. A boxed warning had been added that characterizes the reported cases of AHF and provides both relative and absolute risk estimates.

These changes are more severe than proposed by Abbott. While Abbott proposed a box warning to highlight the increased risk of AHF, there was no discussion of relative or absolute risk and Cylert was left as first line therapy.

Background

On October 25, 1995, HFD-120 asked the Division of Pharmacovigilance and Epidemiology (DPE) to evaluate the article by Berkovich entitled "Pemoline-associated fulminant liver failure: testing the evidence for causation." (*Clinical Pharmacology and Therepueutics.1995;57:696-698*) and to provide an update on FDA reports of hepatic AEs that have been associated with Cylert use. The Berkovich article was submitted as a 15-Day Adverse Reaction Report on 8/4/95.

On 2/2/96, a consult was received from DPE describing 8 cases of AHF in 5-16 year old domestic users of Cylert. Based upon use estimates from IMS, DPE concluded that the incidence rate (cases per time of Cylert use in person-years) was increased from 6 to 22 fold that of estimates of the background incidence rate (IR) for unexplained AHF in 5-16 year olds in the general population. On 3/14/96, Abbott responded to a 2/20/96 HFD-120 letter providing "a proposal to optimize the use of Cylert in the marketplace, given the low but estimated increased risk of AHF in children". In this response, Abbott estimated that the IR of AHF during Cylert use was 4 times that in the general US population. Abbott also estimated the absolute risk (now putting patients in the denominator) in a range Cylert users years of age.

On 4/12/96, in a response to a HFD-120 request to describe AHF with methylphenidate, DPE found 1 possible case that may have been associated with methylphenidate use. On 4/17/96, DPE responded to the 3/14/94 Abbott absolute risk (AR) estimates and to Abbott's contention that the IR was increased less than DPE estimated (4 fold more than that in the general population). In that response, DPE concluded that Abbott had "substantially underestimated the background rate of fulminant hepatic failure". DPE also estimated that the AR ranged Cylert users assuming no under-reporting.

On 5/28/96, the HFD-120 medical officer responsible for Cylert (Dr. Mosholder), completed his review and recommended that Cylert should be a drug of second choice for ADHD and that labeling should be revised to highlight the increased risk of AHF. He also recommended a "Dear Doctor" letter to notify physicians of the changes. On 6/14/96, HFD-120 issued a letter to Abbott proposing modifications in Cylert labeling to reflect its association with life-threatening hepatic failure. A boxed warning was recommended in addition to changing Cylert's indication to "patients who have failed other treatments for ADHD". The boxed warning included a range of AR estimates of Cylert users assuming that 10% of the actual cases were reported to the FDA.

On 8/1/96, Abbott responded to the HFD-120 letter after having received a copy of DPE's 4/17/94 consult. Abbott's response included a critical review of the epidemiologic methods used by DPE. In that response, Abbott proposed labeling changes that included a boxed warning but made no changes to the *Indication* section other than adding that prescribers should consider the risk of AHF. Abbott agreed to notify physicians of the changes in a "Dear Doctor" letter.

I reviewed Abbott's 8/01/96 response on 9/19/96 and outlined the areas of disagreement between Abbott and DPE. On 9/25/96, DPE responded to Abbott's criticism of their AR estimates by providing more AR estimates based upon Medicaid prescription claims data. I reviewed these new estimates on 10/10/96.

Although there has been significant discussion and disagreement on the general issue of hepatotoxicitiy associated with Cylert's use, these issues are not that complicated, but illustrate

the difficulties in making precise point estimates of either relative or absolute risk based upon spontaneous reporting with uncertain data about the extent of product use. There seems to be little disagreement that the number of cases reported significantly exceeds that expected. In addition, there has been at most, one similar case of AHF reported with methylphenidate despite much greater use providing supporting evidence that the reported cases of AHF associated with Cylert's use represent a strong signal of risk.

To try and clarify some of the issues, I will summarize the points of agreement and then what really is one major point of disagreement between DPE and Abbott.

Points of Agreement

Number and Clinical Nature of Reported Cases

There have been 13 cases of life-threatening AHF reported to the FDA from Cylert's approval in 1975 through June 1996 with 11 of these resulting in liver transplantation and/or death. Of the 13, 10 were domestic cases reported in year old patients. Based upon follow-up with the reporters by Abbott and DPE, there were no explanatory factors for the AHF that developed in these cases. In all cases, the event began at least 6 months after first starting Cylert suggesting that there may be some latency to the risk.

Number of Cylert Prescriptions from approval in 1975 through May 1996

Using IMS's NPA database, there have been an estimated 7,680,000 prescriptions filled for Cylert in domestic patients through May 1996. Using IMS's NDTI database, 72% of the total use was estimated to have been in patients years of age.[1] This gives about 5,529,600 Cylert prescriptions in year olds.

Estimating the Incidence Rate for AHF during Cylert Use

By assuming that each domestic Cylert prescription was for 30 days, there have been an estimated 460,800 person-years (PYs) of Cylert use in year old patients from its marketing in 1975 through May 1996. Taking the 10 reported cases as the numerator and the 460,800 PYs as the denominator, gives an estimated IR of about 1 per 46,080 PYs of Cylert use. If 10% of the actual cases have been reported to the FDA then the IR would be about 1 per 4,608 PYs of Cylert use. Of course, if the average length of Cylert prescriptions was significantly greater than 30 days, then the denominator would have been significantly underestimated and the IR significantly overestimated. In addition, there is no way to estimate the extent of under-reporting that is attributable to either the voluntary nature of spontaneous reporting or the apparent latency in developing AHF with Cylert (meaning that physicians may fail to associate AHF with its use).

1 I reviewed the NPA and NDTI databases in the 9/19/96 review.

Estimating the Background IR of Unexplained AHF in 5-19 Year Olds

I reviewed the various estimates provided by Abbott, DPE and myself in the 9/19/96 review. While there seems to be substantial disagreement between those involved regarding the "best" estimate of the background IR of unexplained AHF in year olds, it actually has little impact on the interpretation of the Cylert AHF signal. Abbott's consultants estimated the background IR at 4 cases per million PYs. DPE estimated it at about 0.5 cases per million PYs and I estimated it at about 1 case per million PYs. While DPE and Abbott's consultant's strongly disagree as to who's estimate is best, my interpretation is that all agree that unexplained AHF is an unusual and probably rare event in a year old.

Estimating the Relative Increase in Risk of AHF associated with Cylert Use

Dividing the IR of AHF estimated for Cylert's use by the background IR estimate provides a RR estimate. Thus, Abbott has estimated the RR at 5.4 and using DPE's estimate of the background for the updated data gives a RR of 43.4. If 10% of the actual cases are reported, then the estimates range from There has been a consistent interpretation of the meaning of these estimates by all involved in that the extent of reporting for AHF and Cylert represents a strong signal of risk.

Points of Disagreement

While there is disagreement about the best background IR for unexplained AHF, there is stronger disagreement about how to estimate the AR. DPE has provided 2 different estimates. The first was made based upon a literature reference that stated that the average duration of use of medication use in ADHD is 2.5 years. Applying this estimate to the 460,800 PYs (most recent data) of estimated Cylert use gives 187,200 Cylert patients that have ever used Cylert giving an AR estimate of 1 per 18,700 Cylert users (10/187,200). In the second DPE estimate that was based upon Medicaid data, the average number of prescriptions per patient was 6.9. Applying this to the 5,529,600 prescriptions estimated in 5-19 year olds would give 801,391 users. The AR then would be 10/801,391 or about 1/80,000 Cylert users. If 10% of the actual cases are recognized and reported

Abbott also estimated the AR. Abbott's consultants took the average number of cases reported per year for 1990-1995 (1.2) and took a range of estimates giving AR While I understood the derivation of 84,255 for the calendar year 1993, I still don't understand where the 295,833 upper limit came from.

In Abbott's 3/14/96 response, it is stated that based upon IMS data, Cylert appears to have 8% of the ADHD market which was defined by use of pemoline, methylphenidate or

dextroamphetamine products. If 5% of the 55,228,000 year old in the US (1994 data) are treated for ADHD, this would give about 221,000 current users of Cylert. From the Walsh marketing database, Abbott estimated that there were 84,255 Cylert users in 1993. Thus, my conclusion is that DPE's lowest estimate of 187,200 Cylert users since its marketing in 1975 is probably too low. While Cylert use has probably increased significantly over the last few years with of its total use being relatively recent, I find this estimate not believable. While DPE tried to estimate conditional AR assuming that patients with less than 6 months of Cylert use should not be counted in the denominator, these estimates are probably even more imprecise.

In my opinion, I recommend that we assume that there have been from about 400,000 to 800,000 Cylert users from its approval in 1975 through May 1996. This would give

If 10% of actual cases are recognized and reported, then the range would . For labeling purposes, I included the lower limit from each range since I don't think the width of the ranges are that important to practitioners for making risk/benefit decisions in this case because they are relatively narrow, and since this estimate is close to Abbott's upper limit. The latency issue has been addressed by describing the clinical nature of the cases.

10-11-96

Greg Burkhart, M.D., M.S.
Safety Team Leader
Neuropharmacological Drug Products

cc:HFD-120\Burkhart\Hardeman\Mosholder\Laughren\NDA nos. 16-832, 17-703

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 29, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Decision on Cylert Hepatotoxicity Action

TO: File NDA 16-832 [Cylert Tablets]
File NDA 17-703 [Cylert Chewable Tablets]

This memorandum explicates the basis for the Division's decision to issue a letter to Abbott Laboratories instructing the firm to 1) revise the Indications, Warnings and Adverse Reactions sections of Cylert [pemoline] product labeling, and 2) to issue a Dear Dr. letter alerting prescribers to and explaining the basis for these changes.

Abbott is being instructed to take these actions without further delay. The Division's action comes after months of protracted discussions and negotiations among ourselves and between the Division and the firm's representatives concerning the significance of the fact that post-marketing reports of fatal or potentially fatal (sufficient to cause liver transplantation) unexplained acute liver failure are many fold more common with Cylert than with Ritalin[1].

Background:

Why concerns arose about Cylert's safety for use

While reporting rate ratios[2] cannot be taken as reliable estimators of

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[1] Ritalin (methylphenidate) and Cylert (pemoline) are CNS stimulants used in the management of a condition known as Attention Deficit Hyperactivity Disorder. Ritalin is far and away the more widely used of the two products.

[2] A surrogate for product specific relative risk; basically, a ratio of the estimated risk of suffering the event of interest that is associated with each of the two products being compared. The estimate of the specific risk for each

relative risk, they may signal the existence of one, especially in circumstances where an adverse finding is unexpected and the reporting rate ratio for the finding is both 1) extremely large, and 2) not readily attributable to a confounding factor (e.g., product specific adverse publicity, confounding by indication, etc.).

Accordingly, although the findings presented in a paper by Berkovich et al (Clinical Pharmacology and Therapeutics. 1995;57:696-698) did not prove that Cylert posed a substantially greater risk of acute liver failure than Ritalin, it raised serious concerns about the possibility. Based on their estimate of the relative use of Cylert [pemoline] and Ritalin [methylphenidate] in Attention Deficit Hyperactivity Disorder [ADHD], Berkovich et al postulated that the risk of fulminant liver failure was 45 fold (point estimate) greater among users of pemoline than that among users of methylphenidate.

Division staff reviewing this report were mindful, of course, that a high relative risk does not invariably constitute a threat of major importance to the public health (i.e,. the absolute risk of injury may be so small as to make the relative risk tolerable, especially in settings where the product carrying the excess risk is a valuable treatment for a serious condition). On the other hand, even when the absolute incidence of a serious event is very low, knowledge of a high relative risk is still of potential importance to individual prescribers and patients, particularly when the product associated with the excess risk offers no documented advantage to other available treatments. Complete and candid exposition of relative risk seems especially important in products advanced for the treatment of ADHD because a substantive proportion of children assigned that diagnosis [3] may not require

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product is constructed from counts of adverse reaction reports (the numerator), typically made to a spontaneous voluntary post-marketing surveillance system, and a quantitative estimate of the extent, typically in person-time, of use of the specific product (the denominator) over the interval of time during which the numerator reports were generated. observed, reported, collected--not always clear).

[3] The diagnosis of ADHD is, to be circumspect, not always made conservatively; accordingly, not every patient who carries a diagnosis of ADHD necessarily requires pharmacological management, let alone exposure to a drug that imposes even a slight excess risk of fatal or potentially fatal injury.

or may only arguably require pharmacological treatment. Accordingly, the Division viewed the report by Berkovich et al an important signal deserving prompt and full examination.

The Division's Response to the signal

In late October of 1995, therefore, the Division sought a consultative review and analysis from DPE of the reports of liver failure that had accumulated in the agency's SRS for Ritalin and Cylert over the course of their marketing history.

The first of several responses to our request of DPE was received in early February of 1996. Essentially, DPE confirmed that the reporting rates for fatal or potentially fatal liver injury were much greater with Cylert than with Ritalin; moreover, Dr. Graham estimated the absolute risk of fatal or potentially fatal liver disease to 35-42/ million users, not far removed from the risk of 1/20,000 estimated by Berkovitch (assumes that around 66,000 children were exposed to Cylert over its 17 year marketing history).

On February 20, 1996, therefore, having informed both Office and Center officials of our plans, we wrote to Abbott to inform them that our analyses of the reporting rate ratio for acute fatal liver failure associated with Cylert and Ritalin, taken in light of the lack of any documented advantage for Cylert vis a vis other products carrying that indication, had led us to conclude that Cylert had "an unfavorable risk benefit ratio." Accordingly, we asked the firm to either withdraw Cylert from the market or provide a "satisfactory rationale[4] for keeping" it on the market.

Within 2 weeks, Abbott responded, agreeing that the matter of Cylert's hepatotoxicity deserved serious scrutiny, but asking for more time as well as background information concerning the various estimates we had employed in our analyses. Subsequently, on March 14, 1996, Abbott provided a more extensive response in which they agreed that the relative risk of acute liver failure was higher with Cylert than with Ritalin, but only slightly so (they estimated the relative risk to be 4 with a CL of 1.19 to 13.9). Abbott also offered an estimate of the absolute risk of acute hepatic failure with Pemoline that ranged from 1 in 89,000 to 1 in 355,000. Accordingly, Abbott

[4] Although the Division's letter did not offer the option, the firm correctly surmised that changes in Cylert labeling might cause us to revise our adverse conclusion about its risks and benefits.

proposed that Cylert could be deemed safe for use if 1) a bolded Warnings statement was added to labeling and 2) prescribers were informed of the change via a Dear Dr. letter.

Given the differences between the firm's estimates of risk and our own, the Division asked DPE to review Abbott's submission. We received a reply indicating that, in the judgment of DPE staff, Abbott had "seriously underestimated the true relative and absolute risk of fulminant hepatic failure associated with pemoline use[5]."

After further internal deliberations, we came to the conclusion that so many uncertainties were associated with the estimates of relative and absolute risk, that we could not justify a demand that Cylert be withdrawn from the market. Accordingly, we issued a second letter to Abbott (June 14, 1996) in which we proposed that Cylert remain on the market, but with labeling that 1) identified it as a treatment of second choice and 2) warned prominently of its capacity to cause acute liver failure.

On June 28, Abbott acknowledged our revised request, but asked for additional time to review the matter with a panel of experts (epidemiologists, clinicians, hepatologists, etc.) they were assembling. On August 1, 1996, Abbott declined to adopt the labeling that the Division had proposed in June, in particular, objecting to the change in the Indications section limiting Cylert to use as a treatment in patients failing to respond to other interventions. Abbott did offer, however, to include information about the risk of acute hepatic failure in the Indications Section and to employ a black box around the Warnings statement describing the risk of acute hepatic failure.

Abbott again justified its rejection of the Division's proposal, at least in part, on grounds that FDA's estimates of the risk (both relative and absolute) of liver failure were unreasonably high. Accordingly, DPE was asked by the Division to review Abbott's critique of their calculations. The DPE reply was provided to the Division on October 3, 1996 (Graham memorandum of 9/25/96); again, DPE argued that the firm was being too sanguine about pemoline's risks.

In an attempt to gain closure on what I feared would become an even more

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[5] Graham, D. 4/17/96 consult

protracted exchange, I asked Dr. Greg Burkhart, the safety unit team leader, to conduct an independent critique of the arguments and assumptions employed in the analyses conducted by both Abbott and DPE.

In two memoranda (dated 10/10/96 and 10/11/96) responding to my request, Dr. Burkhart systematically reviews the arguments that have been used by DPE to estimate both the relative (to Ritalin) and absolute risks of acute hepatic failure associated with the use of pemoline.

The disagreements between the agency and the firm arise, in Dr. Burkhart's view, largely from different assumptions about 1) the extent of use of Cylert and 2) the degree of under-reporting of cases of acute liver failure. The firm's estimate for the number of patients treated with Cylert is, for example, larger than Dr. Graham's.

In sum, when candled closely, both Abbott's estimates and DPE's turn on assumptions that cannot be empirically verified. On the other hand, I am persuaded that the firm's estimates for the extent of Cylert's use are likely to be on the high side. In any case, although I cannot know the extent of the excess risk with precision, I remain persuaded, based on post-marketing reports, estimates of market share and extent of use, etc, that pemoline, in contrast to methylphenidate, causes acute liver failure, albeit at what can arguably be viewed as a low absolute incidence.

Conclusions and Actions taken:

While the absolute risk of acute liver failure associated with the use of Cylert is not sufficient to justify its removal from the market, the evidence bearing on this risk relative to that associated with other marketed treatments for ADHD is more than sufficient to require that Cylert be identified as treatment that should not be used first in management of patients with ADHD.

This conclusion will be conveyed to the firm in a letter that I have drafted by modifying the proposal developed by the Review team (see Attachment I); the labeling text developed by the Team may go as ~~proposed~~ as should the text of the Dear Dr. letter.

/S/

Paul Leber, M.D.
October 29, 1996

cc
NDA 16-832
NDA 17-703
HFD-100 Temple
HFD- I 20/Div File
HFD-120
Laughren
Mosholder
Burkhart
Hardeman

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DRAFT LABELING

U.S. Food and Drug Administration

This is the retyped text of a letter from Abbott Laboratories Pharmaceutical Products Division. Contact the company for a copy of any referenced enclosures.

IMPORTANT DRUG WARNING

December, 1996

Dear Doctor.

This communication is to advise you of a labeling change for Cylert (pemoline, Abbott). A recent review of postmarketing experience with Cylert disclosed ten reports from the U.S. of acute liver failure in children, with additional reports of liver failure in adults and in children from foreign countries.

Based on discussions with the Food and Drug Administration (FDA), Abbott Laboratories has modified the current product labeling to include a boxed warning describing liver failure and to indicate that Cylert should not ordinarily be considered as first line drug therapy for Attention Deficit Hyperactivity Disorder (ADHD). Related changes have been made to the Precautions/Laboratory Tests and the Adverse Reactions/Hepatic subsections of labeling. A copy of the revised package insert is included for your review. The following is the text of the boxed warning.

> Because of its association with life threatening hepatic failure, CYLERT should not ordinarily be considered as first line drug therapy for ADHD (see **INDICATIONS AND USAGE**).
>
> Since CYLERT's marketing in 1975, 13 cases of acute hepatic failure have been reported to the FDA. While the absolute number of reported cases is not large, the rate of reporting ranges from 4 to 17 times the rate expected in the general population. This estimate may be conservative because of under reporting and because the long latency between initiation of CYLERT treatment and the occurence of hepatic failure may limit recognition of the association . If only a portion of actual cases were recognized and reported, the risk could be substantially higher.
>
> Of the 13 cases reported as of May 1996, 11 resulted in death or liver transplantation, usually within four weeks of the onset of signs and symptoms of liver failure. The earliest onset of hepatic abnormalities occurred six months after initiation of CYLERT. Although some reports described dark urine and nonspecific prodromal symptoms (e.g., anorexia, malaise, and gastrointestinal symptoms), in other reports it was not clear if any prodromal symptoms preceded the onset of jaundice. It is also not clear if the recommended baseline and periodic liver function testing are predictive of these instances of acute liver failure. CYLERT should be discontinued if clinically significant dysfunction is observed during its use. (see **PRECAUTIONS**).

If you have any questions, please contact our Medical Services Department at 1-800-633-9110.

Sincerely,

David Pizzuti, M.D.
Divisional Vice President
Medical Affairs and Pharmaceutical Ventures

Enclosure: Cylert (pemoline) Product Information, Abbott Laboratories

Abbott Laboratories
Pharmaceutical Products Division
200 Abbott Park Road
Abbott Park, IL 60064-3537

Return to Summary

MEDWATCH

FDA HOME PAGE COMMENTS DISCLAIMER

ABBOTT

Pharmaceutical Products Division

ORIGINAL

Abbott Laboratories
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November 4, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

NOV - 5 1997

RECEIVED HFD-120

17-703 NDA SUK-013

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

APPEARS THIS WAY ON ORIGINAL

Re: Cylert® (pemoline)
NDA 16-832
NDA 17-703

GENERAL CORRESPONDENCE
Revised Package Insert
Labeling of 12/96

Dear Dr. Leber:

This letter is in response to a recent telephone conversation with Anna Marie Weikel requesting resubmission of the revised package insert for Cylert® originally submitted in our February 12, 1997 submission. Enclosed with this correspondence you will find the revised Cylert® package insert, 03-4735-R18, revised in December 1996.

ON ORIGINAL

Should you have any questions concerning this submission, please do not hesitate to contact me.

Sincerely,

Matthew A. Biondi
PPD Regulatory Affairs
D-491, AP6B, (847) 938-0623
Fax (847) 937-8002

APPEARS THIS WAY ON ORIGINAL

11/18/97
Noted
/S/

Copy of Correspondence to:

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DRAFT LABELING