CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 11522, S010

APPROVAL LETTER

NDA 11-522 / S-010

FEB 13 1996

Richwood Pharmaceutical Company, Inc.
Attention: William A. Nuerge
Chief Operating Officer
7900 Tanner's Gate Drive, Suite 200
Florence, KY 41042

Dear Mr. Nuerge:

Please refer to your supplemental new drug application of September 21, 1995 (S-010), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adderall (dextroamphetamine saccharate, dextroamphetamine sulfate, amphetamine aspartate, and amphetamine sulfate) 10 mg and 20 mg tablets.

Supplemental application S-010 consists of the resubmission and provides critical analyses for the quantitation of d- and l-amphetamine, and updated manufacturing, controls and test procedures. The supplemental application also provides draft labeling revised in response to the Federal Register notice of August 8, 1970 (DESI 5378), classifying this drug effective for use in the treatment of narcolepsy, attention deficit disorder with hyperactivity, and exogenous obesity.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended with the labeling changes listed below. Accordingly, the application, with these labeling revisions, is approved effective as of the date of this letter. This action also approves this application on the basis of effectiveness of the drug as well as safety and supersedes the Federal Register notice of September 25, 1973, thus re-establishing the approval of NDA 11-522.

The labeling revisions, as agreed to by Rob Falconer of your firm during his telephone conversation with Steven D. Hardeman, R.Ph., of this agency on January 26, 1996, are as follows:

1. The statement currently placed in Warnings, "*Clinical experience suggests ... growth should be monitored during treatment.*" should not be repeated under Precaution--Pediatric Use.

2. The statement under Precautions that FD&C Yellow #6 causing allergic reactions is unnecessary and should be deleted, as this statement applies to FD&C Yellow #5 rather than #6.

3. Under Adverse Reactions--Cardiovascular, the statement, "There have been isolated reports of cardiomyopathy associated with chronic amphetamine use," should be added

4. The treatment of overdosage section should be updated, as follows:
(additions are in redline font, deletions are in strikeout font)

OVERDOSAGE:

TREATMENT--Consult with a Certified Poison Control Center for up to date guidance and advice: Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine (Regitine®, CIBA) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

We also have the following request and acknowledgment regarding chemistry and manufacturing controls:

1. We request that you place all 6 validation batches on long-term stability at ambient (i.e, either 30°/ambRH or 25°/60%RH) conditions. Please provide your stability protocol and commitment (i.e. storage conditions, sampling times, and tests to be performed).

2. As requested, a 24-month expiration dating period at ambient conditions is acceptable.

These revisions are terms of the supplement approval. Marketing the product before making, exactly as agreed to, the revisions in the products's labeling may render the product misbranded and an unapproved new drug

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed or 6 months from the date of this letter. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 11-522 / S-010. Approval of this labeling by FDA is not required before it is used. Should additional information relating to the safety and effectiveness of the drug become available, further revision of that labeling may be required.

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

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

Sincerely yours,

Robert Temple 2/12/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 11522, S010

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 11-522 (Obetrol/Adderall)
Sponsor: Richwood Pharmaceutical
Drug: Dextroamphetamine saccharate/amphetamine aspartate/dextroamphetamine sulfate/amphetamine sulfate
Material Reviewed: Prepublication draft of a Medical Letter article regarding Adderall and other drugs for attention deficit hyperactivity disorder
Date Received: October 17, 1994

I. Material Reviewed

The Office of Health Affairs has asked our Division to comment upon this Medical Letter draft article, "Adderall and other drugs for attention deficit hyperactivity disorder." Adderall is a combination amphetamine product (see above) which was formerly called Obetrol. (I understand that this product may be subject to a compliance action; apparently it is being marketed without an approved NDA. This information, however, is still confidential.)

The draft article begins with a reference to the "vigorous" promotion of Adderall, and concludes by stating that no literature studies are available to support the safety and efficacy of the medication, or the claim that its effect lasts throughout the school day after one dose. The body of the article reviews the pharmacotherapy for attention deficit hyperactivity disorder (ADHD), and presents a balanced although brief summary of important clinical considerations. The information on dosing, pharmacokinetics and adverse effects for the most part agrees with what is commonly cited in the literature or described in the labeling for the psychostimulants. Some items which might deserve mention as adverse effects are toxic psychosis and cardiovascular effects; also, there is no reference to the fact that psychostimulants are associated with many drug-drug interactions (e.g., with monoamine oxidase inhibitors, pressors, etc. as noted in their respective labels). The article does not mention lowering of the seizure threshold as an adverse effect; however, this is a somewhat controversial topic and the literature on this purported effect of the stimulants is mixed. Regarding efficacy, the article states that no controlled studies have been published to support the efficacy of Desoxyn or Adderall in ADHD. Nonetheless, Desoxyn is approved for this indication. As Desoxyn was approved in 1943, however, the particular clinical trial data which led to approval may not be readily accessible. A few compounds which have been used "off label" in ADHD are also mentioned (clonidine, desipramine, buproprion), but the article is not inordinately promotional regarding these drugs.

II. Conclusions and Recommendations

On balance, the draft article is an objective and rational summary of pharmacotherapy for ADHD.

Suggested comments for letter to Dr. Mark Abramowitz, editor of The Medical Letter

We have reviewed your draft article on "Adderall and other drugs for attention deficit hyperactivity disorder" and we believe that it presents a balanced and fair summary of pharmacotherapy for this disorder. We have no corrections to suggest, but some minor

additions might be in order. Space permitting, toxic psychosis and cardiovascular effects probably deserve mention in the paragraph on adverse effects; likewise, reference could be made to the fact that many drug-drug interactions, some potentially serious, occur with the psychostimulants (e.g., with monoamine oxidase inhibitors, pressors, anticonvulsants etc: see their respective package inserts). Additionally, with respect to the use of non-stimulant drugs, it could be noted that clinical experience with such drugs is limited compared to the extensive experience with psychostimulants, and that non-stimulants are not considered first line drugs; no non-stimulant drugs have been approved by FDA for this indication.

We greatly appreciate the opportunity to comment upon this manuscript, and if we may help by providing commentary on other drafts in the future, please do not hesitate to ask.

10/19/94

Andrew Mosholder, M.D.
Medical Officer, HFD-120

orig NDA 11-522 Div File
cc: PLober/TLaughren/SHardeman/AMosholder

11-20-94
I agree with the above review & comments for Ritalin.
Thomas P. Laughren, MD

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 11522, S010

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Doc. Rm

MEMORANDUM

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

DATE: November 1, 1994

FROM: Steven D. Hardeman, R.Ph. SH 11/1/94
Consumer Safety Officer
Division of Neuropharmacological Drug Products, HFD-120

THRU: Thomas Laughren, M.D.
Psychiatric Group Leader
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: NDA 11-522 Obetrol® / ADDERALL™ (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate, amphetamine aspartate) 10 mg and 20 mg Tablets Administrative History

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

During my conversation of May 13, 1993, with Peggy Spade (NY District - FDA) and Brad Williams (Office of Compliance), the approval status of NDA 11-522 (Obetrol®) came into question. I attempted to conduct a detailed administrative review of the NDA, however, no record of the original file could be located. The Division Document Room Personnel insist that the NDA is withdrawn and the file has been retired by the Central Document Room. Subsequent efforts to retrieve the application were unsuccessful. I located a personal file and the following issues emerged:

1. In the Federal Register notice of February 12, 1973, the Commissioner announced an opportunity for hearing on his proposal to withdraw approval of new drug applications for combination amphetamines.

2.

3. The Commissioner, based on the review of the medical documentation offered to support the claims of safety and efficacy for Obetrol tablets, found that Rexar Pharmacal Corp. failed to present substantial evidence of effectiveness. Approval of NDA 11-522 was withdrawn by the Commissioner's order effective on October 5, 1973. Notice of the ruling was published in the Federal Register of September 25, 1973, "Final Order on Certain Combination Anorectic Drugs". (attachment 1)

4.

5.

6.

7. In his telecon of February 26, 1982, to John Geiger (compliance), Dave Barash, CSO, explained that the product was being marketed without an approved NDA, and asked what action would be taken. An inspection took place on January 28, 1982, and no validation data was available. (attachment 3)

8. The sponsor (Thad Demos - Richwood Pharmaceuticals) contacted me via phone in early 1994 to request the status of the review of their reformulation supplement. I informed him of the following:

   a. It appears that the NDA was withdrawn by the commissioner in a Federal Register Notice in September 1973.

   b.

   c. Aside from references in COMIS and a personal file, the Division has no records on the NDA. I informed him that COMIS is merely a document tracking database.

   d. I advised that he should request a complete (unpurged) copy of all documents including supplements, amendments and annual reports under the Freedom of Information Act. I reminded him that he must also provide proof of ownership of Rexar's NDA. He informed me that Richwood had purchased Rexar.

   e. I informed him that Rexar (Richwood) is in a precarious situation in that they are unable to provide documentation of their NDA's approval status and appear to be marketing without an approved NDA.

9. In the letter of October 21, 1994, the sponsor requested copies of material contained in my personal file. In my letter of October 26, 1994, I forwarded a copy of the September 25, 1973, Federal Register notice and a copy of the Division's letter of September 9, 1980. (attachment 4)

10. Following the sponsor's initial inquiry, I contacted Doug Ellsworth and Lee Drapkin (compliance) to ask the status of compliance actions for this product. In his phone call of September 23, 1994, Larry Daurio of FDA NY District Compliance informed me that a "Warning Letter" for the Obetrol products was to be issued to the sponsor on October 24, 1994. (attachment 5)

11. In the September 1994 edition of the Journal of the American Academy of Child and Adolescent Psychiatry, Richwood Pharmaceuticals (new owners of Rexar Pharmacal) is promoting Obetrol (renamed ADDERALL) as a unique once a day alternative in the treatment of ADHD. (attachment 6)

12. In a consult request from HFY-1/Office of Health Affairs, the Division was asked to comment on the Medical Letter draft article "Adderall and Other Drugs for Attention Deficit Hyperactivity Disorder". (attachment 7)

13. A copy of the ADDERALL advertising and a copy of the "Warning Letter" was forwarded to Sherry Danese (DDMAC) on October 31, 1994.

cc:
HFD-120
HFD-120/Leber
/Laughren
/Purvis
/Hardeman

November 1, 1994

C:\DOCS\NDA\OBETROL\OBETROL.MEM

MEMORANDUM FOR RECORD

Attachment 1

D-120 NDA 11-522

additive will not have a significant environmental impact. Copies of the environmental impact analysis report are available in the Office of the Assistant Commissioner for Public Affairs, Rm. 15B-42 or the Office of the Hearing Clerk, Food and Drug Administration, Rm. 6-86, 5600 Fishers Lane, Rockville, MD 20852.

Dated September 12, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-20209 Filed 9-24-73;8:45 am]

[DESI 5378; Docket No. FDC-D-682; NDA 11-522]

CERTAIN COMBINATION ANORECTIC DRUGS

Final Order on Objections and Request for a Hearing Regarding Withdrawal of Approval of New Drug Applications

In the FEDERAL REGISTER of August 8, 1970 (35 FR 12652) the Commissioner of Food and Drugs published a statement of policy (21 CFR 130.46) concerning amphetamines for human use. The statement contained the findings of the Food and Drug Administration based upon reports received from the National Academy of Sciences-National Research Council (NAS-NRC) Drug Efficacy Study Group. Also published in the FEDERAL REGISTER of August 8, 1970 (35 FR 12678) was a notice (DESI 5378) on drugs containing amphetamines and their salts, stating that the drugs were regarded as possibly effective for their claimed anorectic effect and lacked substantial evidence of effectiveness for their other labeled indications. The statement of policy also contained the findings of the Commissioner that because of the extensive use of the drugs in the treatment of obesity, and their stimulant effect on the nervous system, they have a potential for misuse and actual abuse, and production data indicated that amphetamines are produced and prescribed in quantities greatly in excess of demonstrated medical needs. As a condition for continued marketing of amphetamines, the statement of policy required relabeling as specified and the submission of a new drug application (NDA) within one year for all such drugs not then the subject of NDA approval. Holders of approved NDAs were required to submit additional evidence of safety and substantial evidence of efficacy in the form of adequate and well-controlled clinical investigations.

On February 12, 1973, the Commissioner published in the FEDERAL REGISTER (38 FR 4249) a final order stating that there was a lack of substantial evidence of effectiveness for, and a recognized potential for the abuse of, fixed combination drugs for anorectic use which contained, among other ingredients, amphetamine, methamphetamine, or dextroamphetamine. In addition, the Commissioner found that alternative therapeutic measures which are safe and effective are available for use. The Commissioner also stated in the final order that a mixture of dextroamphetamine and amphetamine is ordinarily regarded as a single drug entity. A similar conclusion as to a mixture of dextroamphetamine and methamphetamine, and/or amphetamine and methamphetamine, was not made. In § 3.85 (21 CFR 3.85) the Food and Drug Administration set forth a policy on fixed-combination drugs for prescription use requiring that each drug in a fixed-combination drug contribute to the claimed effect of the drug; section IV, infra. Therefore, drugs containing combinations of amphetamine and methamphetamine and/or dextroamphetamine and methamphetamine, are fixed combination drugs. The final order also stated that a proposal to withdraw approval of such combination drugs for anorectic use was published elsewhere in the same issue of the FEDERAL REGISTER.

In a notice in the FEDERAL REGISTER of February 12, 1973 (38 FR 4279), the Commissioner announced an opportunity for hearing on his proposal to withdraw approval of new drug applications for the combination amphetamine or other anorectic drugs. This notice was based on evaluation of data submitted pursuant to the FEDERAL REGISTER notice of August 8, 1970 (35 FR 12678). This data was found, after review, not to provide substantial evidence that the drugs named in the FEDERAL REGISTER notice of February 12, 1973, were effective as fixed combination for their claimed anorectic uses. Based on this lack of substantial evidence of effectiveness of the drugs as fixed combinations, the recognized potential for abuse of these combination drugs, and the availability of alternative therapeutic measures which are safe and effective, the named drugs were also found to be lacking in proof of safety. The Commissioner further found that the data submitted in response to the FEDERAL REGISTER notice of August 8, 1970, did not support a contention that the combination products decrease the incidence or severity of side effects associated with the abuse potential of the single entity anorectic drug. Notice was therefore given to holders of the named new drug applications and all other interested persons, including those marketing similar, identical or related drugs (§ 130.40 (21 CFR 130.40)) that the Commissioner proposed to withdraw approval of these new drug applications based on a lack of substantial evidence of effectiveness and a lack of proof of safety. All holders of the NDA's and persons marketing similar, identical or related drugs, and other interested persons were invited to request a hearing on the proposed withdrawals and to submit with such request a well organized and full-factual analysis of the clinical and other investigational data they were prepared to prove in support of their opposition to the withdrawal of the named NDA's and any such similar, identical or related drugs. The notice stated that if substantial evidence of effectiveness and evidence of safety was received for any of the named drugs, or for similar, identical and related drugs, the notice would be rescinded as to such drugs.

In response to the notice in the FEDERAL REGISTER of February 12, 1973, requests for a hearing were received from four persons for five drugs. The persons and the drugs were named in the FEDERAL REGISTER notice of March 30, 1973 (38 FR 8290). The subject final order concerns only two of those persons requesting hearings.

Rexar Pharmacal Co., 306 Rockaway Ave., Valley Stream, NY 11582, requested a hearing for the drugs Obetrol-10 and Obetrol-20 Tablets (NDA 11-622). These drugs are the subject of an NDA which was made conditionally effective on July 24, 1959, and fully effective on February 23, 1960. The Obetrol drugs had been reviewed by the NAS-NRC and found to be possibly effective as an adjunct in the management of some forms of obesity in which an appetite depressant is indicated. The NAS-NRC finding was incorporated into the August 8, 1970 FEDERAL REGISTER notice discussed above (35 FR 12678).

Delco Chemical Co., 7 McQuesten Parkway North, Mount Vernon, NY 10550, requested a hearing for the drugs Delcobese Sustained Release Tablets and Capsules and Delcobese Tablets and Capsules. Pursuant to the August 8, 1970 FEDERAL REGISTER order, the Commissioner received from Barrows Pharmacal Inc., 300 Prospect St., Inwood, NY 11696, four new drug applications on the following dates for the following drugs: March 15, 1971, NDA 17-161, Delcobese Tablets, 5 mg., 10 mg., 15 mg., and 20 mg.; March 15, 1971, NDA 17-161, Delcobese Capsules, 5 mg., 10 mg., 15 mg., and 20 mg.; March 26, 1971, NDA 17-160, Delcobese Sustained Release Capsules, 5 mg., 10 mg., 15 mg., and 20 mg.; and June 24, 1971, NDA 17-159, Delcobese Sustained Release Double-Layer Tablets, 5 mg., 10 mg., 15 mg., and 20 mg. All four of the drugs consist of a combination of amphetamines and methamphetamines. No data was submitted in support of the efficacy of these combination drugs; the sponsor merely paraphrased the conclusions stated in the August 8, 1970 FEDERAL REGISTER notice in support of the safety and efficacy of the drugs for use as anorectics and in treating narcolepsy and minimal brain dysfunction in children.

Due to the large number of new drug applications received pursuant to the August 8, 1970 FEDERAL REGISTER order, a review and evaluation of the new drug applications submitted by Barrows was delayed. Barrows was notified of this delay by a letter from the Food and Drug Administration on February 23, 1973. On January 18, 1973, a letter was sent to Barrows from J. Richard Crout, M.D., Acting Director, Office of Scientific Evaluation, Bureau of Drugs, stating the conclusion of the Food and Drug Administration that the four new drug applications submitted by Barrows could not be approved because the submissions

...nified to demonstrate that each component of the drug makes a contribution to the claimed effect and that the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug (21 CFR 3.86). In response to this letter, Delco Chemical Co., Inc., 7 McQuesten Parkway North, Mount Vernon, NY 10550, notified the Food and Drug Administration that it was reformulating the products subject to the submitted new drug applications into "single entity amphetamine preparations." No further communication has taken place.

The other drugs named in the FEDERAL REGISTER notice of March 30, 1973, will be the subject of orders ruling on the requests for hearings to be published in the FEDERAL REGISTER at a future date.

I. *The Drugs* a. Obetrol 10 and Obetrol 20 Tablets, respectively contain 2.5 mg. each or 5 mg. each of methamphetamine saccharate, methamphetamine hydrochloride, amphetamine sulfate, and dextroamphetamine sulfate per tablet.

b. The four Delcobese drugs are combinations of dextroamphetamine sulfate, methamphetamine hydrochloride, methamphetamine adipate and amphetamine sulfate.

II. *Recommended Uses* a. Obetrol 10 and Obetrol 20 Tablets are recommended in exogenous obesity as a short-term (a few weeks) adjunct to a regimen of weight reduction based on caloric restriction.

b. The Delcobese drugs are recommended in exogenous obesity, as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, and in the treatment of narcolepsy and minimal brain dysfunction in children.

III. *The Data to Support Claims of Effectiveness* A. *Obetrol 10 and Obetrol 20 Tablets* 1. *Published Studies.* Rexar has submitted five literature reprints which it contends support the efficacy of Obetrol Tablets. For the following reasons, these studies are not substantial evidence of the effectiveness of Obetrol Tablets since they are not adequate and well-controlled clinical investigations.

a. *Modern Management of Obesity—The "Social Diet"*, Milton Plotz, M.D., *J.A.M.A.*, July 28, 1956, Vol. 170, pp. 1513-1515. This report is substantially a discourse on the causes of obesity and the various methods of treating the condition. It merely reports that the author feels that some investigators, including himself, have established a genuine therapeutic action with certain drugs in promoting weight reduction. There is no actual clinical data presented, no discussion of the investigations as to size of the studies, no controls or statistical methods, and no reference to the composition of the drugs that were employed in the investigations, as required by § 130.12(a)(5) (21 CFR 130.12). The author mentions that Obetrol was used in "this" study, but the reference to which study is unclear. The criteria for establishing that a study is adequate and well-controlled, set forth at § 130.12(a)(5), have not been met.

The study is, on its face, insufficient to support any claim of effectiveness for the Obetrol Products. The Commissioner finds that this article is not substantial evidence of the efficacy of Obetrol Tablets.

b. *The Treatment of Obesity in Patients With Cardiovascular Disease*, Franklin Simon, M.D. and Arthur Bernstein, M.D., *Angiology*, Vol. 12 No. 1, January, 1961, 32-37. This is a report of the obesity problem in the United States and a study conducted with Obetrol.

The study reported consisted of 100 patients who were seen by the investigators for "varying" periods of time. The authors stated the test was conducted for two months, an "appropriate" period of time. Why the two months was "appropriate" is not stated. The standard for determining "overweight" was given as "overweight by any standard used." Both Obetrol 10 and Obetrol 20 were administered, with dosage and time of administration altered to conform to individual requirements.

No attempt was made to use any controls in the study. The investigators reported that a placebo substitute was attempted with twenty-five patients after four weeks of treatment, but this type of placebo employment is not a placebo control contemplated by § 130.12(a)(5)(ii)(a)(4)(iii), since the regulation requires that the test drug be compared with the results of a patient group to whom a placebo, in all respects physically identical to the test drug, has been administered throughout the study. The subject study did not comply with the regulation.

The patient population was made up of patients some of whom had some sort of cardiovascular disease with or without diabetes, some with diabetes alone, and some with no other disease conditions. There is no information as to suitability of the patients to be included in a study to determine the effectiveness of an anorectic, and no assurance of comparability of the test group with a control group, since a control group was not employed (§ 130.12(a)(5)(ii)(a)(2)(i) and (iii)). Because of the great variations in the physical conditions of the patients and the other medications they were taking, and the variations of dosage and duration of administration reported by the authors, any specific finding by the investigators related to the effectiveness of Obetrol is of questionable value.

Section 130.12(a)(5)(ii)(a)(5) requires that "a summary of the methods of analysis and an evaluation of the data derived from the study, including any appropriate statistical methods" be submitted. No such data is presented in this study. Therefore, it is not possible to evaluate the analytical and statistical methods employed in order to determine the validity of the results and the investigator's conclusions.

The results of the study were stated in general terms of the total number of pounds lost, with an average being assigned to each patient. No actual patient results were stated. The investigators state that the range of weight loss varied from "almost nothing" to 25 pounds. The authors admit that their results are "made up of combining the good with the bad, the effective with the ineffective weight reducer." Thus, it is impossible to draw any meaningful conclusions as to the efficacy of Obetrol from the study because full reports of patient data obtained from the study are not presented as required by § 130.12(a)(5)(ii)(a)(5).

In addition, since Obetrol is a combination drug within the meaning of § 3.86, the investigators must show that both the amphetamine and methamphetamine components of the drug contribute to the drug's purposed effect. No such showing was made in this study.

The Commissioner finds that this study is not substantial evidence of the effectiveness of Obetrol Tablets.

c. *Treatment of Obese Diabetics and Arteriosclerotics*, Arthur Bernstein, M.D. and Franklin Simon, M.D., Reprint from *Clinical Medicine*, May, 1961, pp. 1-6. This is another report of the study discussed in b, above. It contains no more patient information or data than does the other report, and no statistical analysis. For the reasons stated above, the Commissioner finds this study is not substantial evidence of the effectiveness of Obetrol Tablets.

d. *Use of an Amphetamine-Combination Drug in an Anti-Obesity Clinic*, Merrill Berman, M.D. and Ian Anderson, M.D., *Mid. St. Med. J.*, Jan., 1963, pp. 22-31. This is a report of study conducted with Obetrol-10 Tablets. The patient population numbered 43; the only medical problem of the group was obesity. The drug was tested in 25 patients and compared with 18 patients to whom no medication was administered. The authors stated that "the final outcome of this study will await its ultimate re-evaluation when the patients are reviewed one year from the time they entered the clinic program."

The patients were selected at random, and randomly placed on either the drug or no treatment. Both test and control patients were weighed each week, given nutritional counseling and participated in the same group discussions. The results obtained showed that the group to whom the drug had been administered lost an average of 20.2 pounds over a ten week period, while the control group lost an average of 9.81 pounds over the ten week period. The actual weight loss for each patient is tabulated. The authors concluded that "the group on the amphetamine preparation was able to lose twice as much, on the average, as the control group."

The study is deficient in several respects. First, the degree of overweight of the patients is not specified. Second, the method of randomizing the selection of the patients is not stated, nor is a table of random numbers presented. (§ 130.12(a)(5)). Data is not presented as to the number of entrants in the study and the

number of dropouts. This data is necessary both in order to demonstrate that equal numbers of patients were placed in each group and to follow up on these patients to ascertain why they dropped out. Finally, the analytical technique for evaluating the results is not described making it impossible to establish the significance of the differences of treatment of the two groups (§ 130.12(a)(5)(ii)(a)(4)).

In adition to the above deficiencies, the study is not adequate and well-controlled to establish the efficacy of Obetrol for the following reasons. As pointed out by the investigators in this and the other studies submitted by Rexar, one of the major factors contributing to obesity, and crucial in its treatment, is the psychological condition of the patient. In order to conduct an adequately controlled test with an obesity drug, it is imperative that placebo controls as set forth in § 130.12(a)(5)(iii)(a)(4)(iii) be employed so that all patients think that they are receiving some medication in order to adequately compare the test and control groups. No treatment controls are insufficient in this type of study since a placebo has a definite and significant effect in obesity studies (§ 130.12(a)(5)(ii)(a)(4)(i)). As with all placebo studies, true double blinding is required. Thus, a third party must package both the active drugs and the placebos in containers which are indistinguishable and which can only be identified by code numbers known only to the third party. The placebos and drugs must be physically indistinguishable to both the physician and the patient. Only in this manner will the study result in neither the physician nor the patient being aware, at the time of treatment, which patient is receiving the drug or the placebo. This is required so that physician and patient expectations do not bias the study. Double blinding was not done in this study.

Finally, the study was not conducted in such a manner that the Investigators demonstrated that both the amphetamine and the methamphetamine constituents of Obetrol contributed to its anorectic effect. Such a showing is required to establish the efficacy of a fixed combination drug such as Obetrol. In order to show the contribution of each ingredient it is necessary to have four test groups—one on the combination drug, one each on each of the active ingredients, and one on a placebo. This was not done (§ 3.86).

The Commissioner finds that this study is not substantial evidence of the efficacy of Obetrol Tablets.

c. Comparison of Weight Losses With Their Reducing Regimens-Diet Therapy, Phenmetrazine, and . . . Obetrol, Merrill Berman, M.D. and Ian Anderson, M.D., *J. Am. Geriatric Soc'y*, Vol. 14 No. 6, pp. 623-630.

In this study, 88 overweight female outpatients in the Anti-Calory Clinic were randomly divided into three groups, unequal in size: 18 to whom no medication was administered; 41 to whom phenmetrazine hydrochloride was administered; and 29 to whom Obetrol was administered. There is no explanation given for the variation in the number of subjects in each group. The no treatment group had an obesity duration of 10 years or longer in all cases; the other two groups had a long obesity duration. There is no reason given why the 10 years for the no-treatment group is significant or why the lack of specific duration of obesity for the other two groups is significant.

The results of the study showed an average loss of 2.0 pounds in two weeks, 4.2 pounds in four weeks, 6.4 pounds in six weeks, 8.6 pounds in eight weeks and 10.3 pounds in 10 weeks for the controls. For the phenmetrazine group, the average weight loss was 3.6 pounds in two weeks, 6.6 pounds in four weeks, 9.7 pounds in six weeks, 11.9 pounds in eight weeks and 13.8 pounds in 10 weeks. Finally, the Obetrol group averaged a weight loss of 5.0 pounds in two weeks, 9.5 pounds in four weeks, 13.8 pounds in six weeks, 18.3 pounds in eight weeks and 22.6 pounds in 10 weeks.

The results are not meaningful since there are no data relevant to the amount and frequency of medication. The degree of overweight of the patients is not given so that an objective comparison of the test subjects' weight loss is not possible. There is no method of randomizing the selection of the subjects stated, nor is a table of random numbers presented. The analytical technique for evaluating the results is not described so that the significance of the differences of treatment of the various groups cannot be established (§ 130.12(a)(5)(ii)(a)(4), and (a)(5)(ii)(a)(4)(i), (iii), and (iii)).

As with the study discussed in paragraph d. above, the necessary placebo is not present. The "active drug" control is insufficient because the administration of a placebo would not be contrary to the interest of the patient (§ 130.12(a)(5)(ii)(a)(4)(iii)). Furthermore, the follow-up study, in which only Obetrol was used, and then, only as needed, has no significance for purposes of demonstrating the efficacy of Obetrol. The study is not adequately double blinded for the reasons set forth in d above. Finally, there are no data to show that both the amphetamine and methamphetamine constituents of Obetrol contributed to the efficacy of the drug (§ 3.86).

The Commissioner finds that this study is not substantial evidence of the efficacy of Obetrol Tablets.

2. *Unpublished Studies.* a. *The Leberco studies.* Rexar also submitted two studies conducted by Leberco Laboratories in 1972. The studies are apparently acute toxicity studies. The first was conducted with Dexedrine. The purpose of this uncontrolled study is not stated. The target population ostensibly consisted of "normal, healthy albino rats", although the criteria for determining the condition of the rats is not stated (§ 130.12(a)(5)(ii)(a)(2)(i)). The animals were fed 10 milligrams of Dexedrine per cc of a suspension substance for an unspecified period of time, possibly only once, although this is not clear. The investigator concluded that "when the above results were calculated according to the method of Behrens, the LD_{50} was established to be 112 milligrams per kilogram of rat. This is equivalent to 8,720 milligrams in a 60 kilogram human being."

The second study was conducted with 800 tablets of "Oby-Rex #1", composition not stated. The purpose of this uncontrolled study is not stated. In this study, the target population ostensibly consisted of "normal, healthy albino rats", although the criteria for determining the condition of the rats is not stated (§ 130.12(a)(5)(ii)(a)(2)(i)). The test animals were fed 40 milligrams of Oby-Rex #1 per cc of a suspension substance for an unspecified length of time, possibly only once, although this is not clear. The investigator concluded that "when the above results were calculated according to Behrens, it was found that the LD_{50} of the test material is 283 milligrams per kilogram of rat. This is analogous in the human to 16,890 milligrams".

Rexar states that these two studies were comparative, but fails to state what was being compared, and the results of any such a comparison are nowhere stated. Furthermore, the results are not confirmed by clinical data since they are only acute data. The results of such animal studies cannot be extrapolated to man. Therefore, these studies do not prove the safety of Obetrol Tablets in human beings.

The two studies do not establish either the effectiveness or safety of Obetrol. Indeed, whether or not the "Oby-Rex #1" is of the same composition as Obetrol is not stated. The Commissioner finds that these studies do not constitute evidence of safety or substantial evidence of the efficacy of Obetrol Tablets for its intended use.

b. *The Nedelman study.* In a letter dated September 21, 1971, Rexar was advised by the Food and Drug Administration that a proposed clinical protocol for a double-blind efficacy study of Obetrol was deficient in several respects; several requirements for the study to be adequate and well-controlled were provided to Rexar. One of these requirements was that Rexar "should provide for acquiring data on the contributions of the individual constituents to the total claimed effect for the drug." Rexar submitted with its request for a hearing, a copy of a protocol of a study to be conducted with Obetrol for Rexar by Medical and Technical Research Associates, Medford, MA, dated January 28, 1972. There is no mention in the protocol of acquiring data on the contribution of the individual constituents to the total claimed effect for the drug. The protocol only provided for two test groups: one to whom Obetrol would be administered, and one to whom placebo medication would be administered. Rexar submitted the results of this study, which was conducted by Philip B. Nedelman, M.D. In the foreword to the study,

), and under authority delegated to the Commissioner (21 CFR 2.120), notice is given that the approval of the New Drug Application for Obetrol-10 and Obetrol-20 Tablets (NDA 11-522) is withdrawn, effective October 5, 1973. This order applies with full force and effect to the Delcobese drugs (§ 130.40).

(Sec. 505, 701, 52 Stat. 1052-1053, 1055-1056, as amended; (21 U.S.C. 355, 371).)

Dated September 17, 1973.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.73-20203 Filed 9-26-73;8:45 am]

[DESI 9418]

[Docket No. FDC-D-602; NDA No. 9-418 etc.]

CERTAIN DRUGS CONTAINING PENTAERYTHRITOL TETRANITRATE IN COMBINATION WITH RAUWOLFIA ALKALOIDS

Notice of Withdrawal of Approval of New Drug Applications

A notice was published in the FEDERAL REGISTER of March 6, 1973 (38 FR 6090), extending to the holders of the new drug applications listed below, and to any interested person who may be adversely affected, an opportunity for hearing on the proposal of the Commissioner of Food and Drugs to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act, withdrawing approval of the listed applications and all amendments and supplements thereto. The basis of the proposed action was the lack of substantial evidence that the drugs are effective for their labeled indications.

NDA No.	Drug	NDA holder
9-418...	Pentaerythrine Tablets, containing pentaerythritol tetranitrate and rauwolfia.	Riker Laboratories, Inc., Subsidiary a 3M Co., 19001 Nordhoff St., Northridge, Calif. 91324
10-084...	Nitrolan Tablets, containing pentaerythritol tetranitrate and rauwolfia.	Dorsey Laboratories, Division of Sandoz-Wander, Inc., Northeast U.S. 6 & Interstate 80, Lincoln, Nebr. 68501.
10-218...	Pentaerythrine Tablets and Pentaerythrine Spansule Tablets, containing pentaerythritol tetranitrate and rauwolfia.	UBV Pharmaceutical Corp., 1 Bernadale Rd., Tuckahoe, N.Y. 10707 (NDA formerly held by Nyseo Laboratories, Inc.).
11-129...	Reserpt Tablets, containing pentaerythritol tetranitrate and rauwolfia.	Westerfield Laboratories, Inc., 2911 Woodburn Rd., Cincinnati, Ohio 45207.

Both Riker Laboratories and UBV Pharmaceutical Corp. (formerly Nyseo Laboratories, Inc.) had previously discontinued their products and elected not to request a hearing. Neither Dorsey Laboratories, Inc. nor Westerfield Laboratories, Inc. filed a written appearance of election as provided by said notice. The failure to file such an appearance constitutes election not to avail themselves of an opportunity for hearing.

In addition to those listed above, three other new drug applications were included in the notice of March 6, 1973. The Lr Pharmaceuticals, Inc., holder of NDA 10-998 for Cartrax 10 and Cartrax 20 Tablets (pentaerythritol tetranitrate and hydroxyzine hydrochloride), American Home Products Corp., holder of NDA 11-423 for Equanitrate 10 and Equanitrate 20 Tablets (pentaerythritol tetranitrate and meprobamate), and Carter-Wallace, Inc., holder of NDA 11-802 for Miltrate Tablets (pentaerythritol tetranitrate and meprobamate), elected to avail themselves of the opportunity for a hearing on their drugs. Their requests for a hearing are under review and will be the subject of a future publication in the FEDERAL REGISTER.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug applications reviewed and are subject to this notice. See 21 CFR 130.40 (37 FR 23185, October 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, MD 20852.

The Commissioner of Food and Drugs pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052, as amended; 21 U.S.C. 355), and the Administrative Procedure Act (5 U.S.C. 554), and under authority delegated to him (21 CFR 2.120), finds that on the basis of new information before him with regard to the drugs, evaluated together with the evidence available to him when the applications were approved, there is a lack of substantial evidence that the drugs will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing finding, approval of new drug applications Nos. 9-418, 10-084, 10-218, and 11-129 and all amendments and supppiements thereto is withdrawn.

Shipment in interstate commerce of the above-listed drug products or of any identical, related, or similar product, not the subject of an approved new drug application, is henceforth unlawful.

Effective date.—This order shall become effective on October 5, 1973.

Dated September 19, 1973.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.73-20196 Filed 9-21-73;8:45 am]

[PAP 3B7856]

SANDOZ COLORS & CHEMICALS

Notice of Filing of Petition for Food Additive

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409 (b)(5), 72 Stat. 1786 (21 U.S.C. 348(b)(5))), notice is given that a petition (PAP 3B7856) has been filed by Sandoz Colors & Chemicals, East Hanover, NJ 07936, proposing that § 121.2526 Components of paper and paperboard in contact with aqueous and fatty foods (21 CFR 121.2526) be amended in paragraph (a)(5) to provide for the safe use of polyamide-epichlorohydrin water-soluble thermosetting resins prepared by reacting adipic acid with diethylenetriamine to form a basic polyamide and further reacting the polyamide with an epichlorohydrin and dimethylamine mixture for use in the manufacture of paper and paperboard intended for use in contact with food.

Dated September 11, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-20200 Filed 9-26-73;8:45 am]

[DESI 11073]

[Docket No. FDC-D-641; NDA 11-073]

WAMPOLE LABORATORIES

Notice of Withdrawal of Approval of New Drug Application

On January 12, 1973, there was published in the FEDERAL REGISTER (38 FR 1404) a notice of opportunity for hearing (DESI 11073) in which the Commissioner of Food and Drugs proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new drug application 11-073 for Vastran Forte Capsules containing niacin (375 mg.) with ascorbic acid, riboflavin, thiamine mononitrate, cyanocobalamin, pyridoxine hydrochloride, and calcium pantothenate; Wampole Laboratories, 35 Commerce Road, Stamford, CT 06904. The basis of the proposed withdrawal of approval was the lack of substantial evidence that this fixed combination drug, offered for hypercholesteremia, will have the effects that it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug application reviewed and are subject to this notice. See 21 CFR 130.40 (37 FR 23185, Oct. 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, MD 20852.

Pursuant to the notice, Wampole Laboratories has reformulated Vastran Forte Capsules into a new product named Wampocap Capsules containing 500 mg. niacin. In the FEDERAL REGISTER of April 18, 1972 (37 FR 7838) and an amendment on March 19, 1973 (38 FR 7378) (DESI 9760), niacin as a single active ingredient was evaluated as effective for hypercholesteremia and hyperbetalipoproteinemia. The amendment of March 19, 1973 stated the following indications:

As adjunctive therapy in addition to diet and other measures in the treatment of hypercholesterolemia and hyperbetalipoproteinemia.

Attachment 2

3 Pages Purged

Unapproved Supplement

Attachment 3

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 2/26/82
FROM: DAVE BARACH		OFFICE
TO: NDA 11-522 (OBETROL)		DIVISION DNDP
SUBJECT: Inspection Request (attached)		

SUMMARY

I called John Geiger, who then referred me to Ray Fazzari regarding the outcome of the inspection request. I was told the inspection took place on January 28, 1982 and no validation data was available. Samples were collected.

I explained that this product is being marketed without an approved NDA (NDA was withdrawn effective 10/5/73) and I asked what action would be taken.

He said that he would analyze the inspection report forward his recommendations to Rudy Apodaca, for regulatory action.

He said I would be informed of any action or correspondence which takes place.

SIGNATURE

DOCUMENT NUMBER

Attachment 4

3 Pages Purged

Unapproved Supplement

Attachment 5

10-31-94 11:26AM FROM FDA NY ..ST. TO 8/3015942859 P004

10.24.94 10:41 AM *CDER/OC/DDLC. HFD-310 P02

w.l. file

5-NYK-95

MEMORANDUM

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

DATE: OCT 19 1994

FROM: Director
Division of Drug Labeling Compliance, HFD-310

SUBJECT: DOC 94-726-063
Obetrol 10 mg. Tablets
Obetrol 20 mg. Tablets

Firm: Richwood Pharmaceutical Co., Inc.
Rexar Pharmacal Division
Valley Stream, New York 11581

TO: Director
New York District, HFR-NE100

5-NYK-95

WARNING LETTER APPROVED

We concur that a Warning Letter should be issued to Mr. Roger Griggs, President of Richwood Pharmaceutical Company, Inc., for the subject products based on violations of the new drug and misbranding provisions of the FD&C Act.

We further concur with the language and information provided in your proposed Warning Letter (copy attached) and have made no changes. However, please include a copy of the September 28, 1973 Federal Register announcement regarding these kinds of products.

Please provide this office with a copy of the Warning Letter that issues and the firm's response.

CSO Contact: Leon Drapkin, HFD-313
(301)594-2073

Bradford W. Williams

Attachment

Warn ltr. file
5-NYK-95

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NEW YORK DISTRICT
850 THIRD AVENUE
BROOKLYN, NY 11232
TEL. (718) 965-5300

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Roger D. Griggs
President
Richwood Pharmaceutical Co., Inc.
Rexar Pharmacal Division
196 Rockaway Avenue
Valley Stream, New York 11581

October 24, 1994

Ref: 5-NYK-95

Dear Mr. Griggs:

This letter is in reference to Obetrol 10 mg. Tablets, and Obetrol 20 mg. Tablets manufactured and distributed by your firm.

The products are currently formulated by your firm as single entity amphetamine products containing Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate. The labeling for the products include the indications: "...Attention Deficit Disorder with Hyperactivity...", and "...Exogenous Obesity...". As such, these products are drugs within the meaning of section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the Act).

The marketing of Obetrol 10 mg. Tablets and Obetrol 20 mg. Tablets is a violation of section 505 of the Act. They may not be introduced or delivered for introduction into interstate commerce under section 505(a) of the Act, since they are new drugs within the meaning of section 201(p) of the Act and no approval of applications filed pursuant to section 505(b) is effective for such drugs, and no Notice of Claimed Investigational Exemption under 505(i) is on file for the drugs.

The drugs are misbranded within the meaning of section 502(f)(1) of the Act in that their labeling fails to bear adequate directions for use for the conditions for which they are being offered and they are not exempt from this requirement under regulation 21 CFR 201.115 since they are new drugs within the meaning of section 201(p) and no approval of applications filed pursuant to section 505(b) are effective for these drugs.

Approval of New Drug Application (NDA) 11-822 for Rexar Pharmacal Co.'s Obetrol 10 mg. and 20 mg. Tablets was withdrawn by the Commissioner's order effective on October 8, 1973. Notice of the ruling was published in the Federal Register of September 28,

1973, "Final Order on Certain Combination Anorectic Drugs". Additionally, the subsequent formulation changes were never approved.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Act and its implementing regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within 15 working days of receipt of this letter, of the action you have taken to discontinue the marketing of these drug products. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. If significant stocks of the drugs remain in trade channels at this time, they should be immediately recalled. We request that your reply include an estimate of the amounts of these products that are in inventory under your control and which remains in distribution channels.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunction.

Your reply should be sent to Compliance Branch, Food and Drug Administration, 850 Third Avenue, Brooklyn, New York 11232, Attention: Laurence D. Daurio, Compliance Officer.

Sincerely,

Edward T. Warner
District Director

Attached:
Federal Register, September 28, 1973,
Certain Combination Anorectic Drugs

FAX COVER SHEET

U.S. FOOD and DRUG ADMINISTRATION
NEW YORK DISTRICT
850 THIRD AVENUE, BROOKLYN, NY 11232

COMPLIANCE BRANCH

DATE: 10/31/94

PAGES (including cover): 4

FROM: Larry Daurio, Compliance Officer, HFR-NE140

Tel. No.: 718-965-5700x870R

Fax No.: 718-965-5117

TO: STEVE HARDEMAN
HFD-20

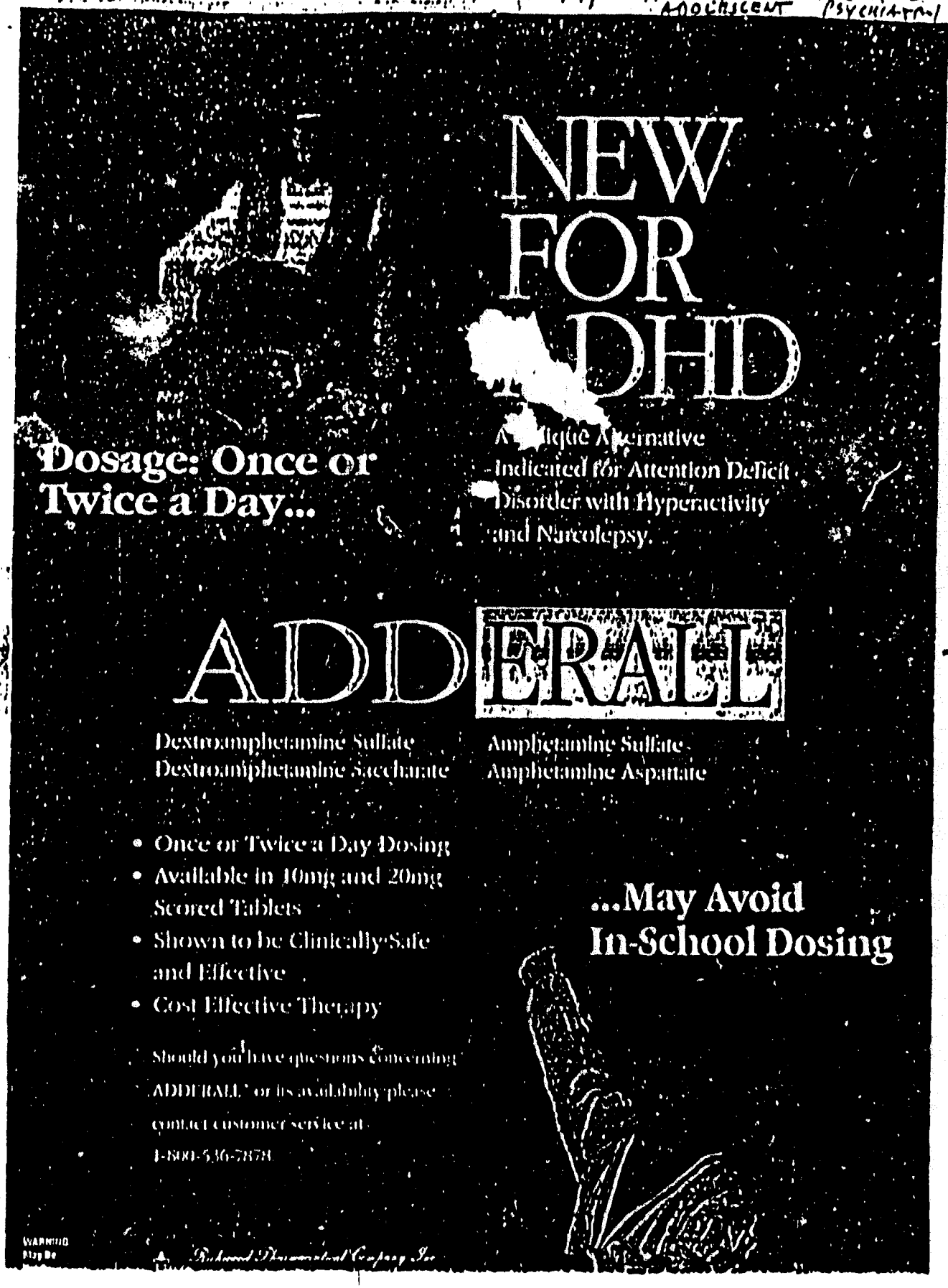
TEL. NO.: 301-594-2850

FAX NO.: 301-594-2859

MESSAGE: as requested
Warning Letter re: Richard's Oberlin

This document is intended only for the party to whom it is addressed and may contain information that is confidential, and protected from disclosure under applicable law. If you are not the addressee, or person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on content of this communication is not authorized. If you receive this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

JOURNAL OF THE AMERICA.
10/94 ACADEMY OF CHILD AND
ADOLESCENT PSYCHIATRY



ADDERALL TABLETS

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. THEY SHOULD THUS BE TRIED ONLY IN WEIGHT REDUCTION PROGRAMS FOR PATIENTS IN WHOM ALTERNATIVE THERAPY HAS BEEN INEFFECTIVE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME IN OBESITY MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

DESCRIPTION: [illegible]

EACH TABLET CONTAINS:	10 mg	20 mg
Dextroamphetamine Saccharate	[illegible]	[illegible]
Amphetamine Aspartate	[illegible]	[illegible]
Dextroamphetamine Sulfate	[illegible]	[illegible]
Amphetamine Sulfate	[illegible]	[illegible]

Inactive Ingredients: Sucrose, Lactose, Cornstarch, Acacia and Magnesium Stearate
Colors: ADDERALL 10 mg contains FD&C Blue #1
Colors: ADDERALL 20 mg contains FD&C Yellow #6 as a color additive

ACTIONS: [illegible]

INDICATIONS: [illegible]

CONTRAINDICATIONS: [illegible]

WARNINGS: [illegible]

PRECAUTIONS: [illegible]

ADVERSE REACTIONS: [illegible]

DRUG ABUSE AND DEPENDENCE: [illegible]

OVERDOSAGE: [illegible]

SYMPTOMS: [illegible]

TREATMENT: [illegible]

DOSAGE AND ADMINISTRATION: [illegible]

HOW SUPPLIED:
ADDERALL 10 mg [illegible]
ADDERALL 20 mg [illegible]

In bottles of 100 Tablets.

DISPENSE IN A TIGHT CONTAINER AS DEFINED IN THE USP
Store at controlled room temperature [illegible]

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for:

Richwood Pharmaceutical Company Inc.

Attachment 6
Preliminary Draft

4 Pages
Purged

Attachment 7

DIV

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: October 20, 1994

OCT 20 1994

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

SUBJECT: Response to Consult Request

TO: HFY-1/Office of Health Affairs

Background Information:

Issue Requiring Response:	Medical Letter article on Adderall, et al
Underlying Documents:	Medical Letter article on Adderall, et al
Date of Request:	10-17-94
Requester:	Carol Kimbrough

Attached Response:

Attached to this memo is the Division's response to your consult request. We have included our review and also a copy of our direct response to the Medical Letter.

cc:
HFD-120/Consult File
HFD-120/TLaughren/PLeber/AMosholder

DOC: MEDLTR.1A

October 20, 1994

The Medical Letter, Inc.
Attention: Mark Abramowicz, M.D.
Editor
1000 Main Street
New Rochelle, N.Y. 10801

Dear Dr. Abramowicz:

Please refer to your letter of October 7, 1994, requesting Agency comments on the draft article "Adderall and Other Drugs For Attention Deficit Hyperactivity Disorder."

We have reviewed your draft article and we believe that it presents a balanced and fair summary of pharmacotherapy for this disorder. We have no corrections to suggest, but some minor additions might be in order. Space permitting, toxic psychosis and cardiovascular effects probably deserve mention in the paragraph on adverse effects; likewise, reference could be made to the fact that many drug-drug interactions, some potentially serious, occur with the psychostimulants (e.g., with monoamine oxidase inhibitors, pressors, anticonvulsants etc: see their respective package inserts).

Additionally, with respect to the use of non-stimulant drugs, it could be noted that clinical experience with such drugs is limited compared to the extensive experience with psychostimulants, and that non-stimulants are not considered first line drugs; no non-stimulant drugs have been approved by FDA for this indication.

We greatly appreciate the opportunity to comment upon this manuscript, and if we may help by providing commentary on other drafts in the future, please do not hesitate to ask.

Sincerely yours,

RLK for PL 10/26/94

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

MEMORANDUM

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

DATE: November 7, 1994

FROM: Steven D. Hardeman, R.Ph.
Consumer Safety Officer
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Telecon of June 20, 1994, with Thad Demos of Richwood Pharmaceuticals in Reference to NDA 11-522 Obetrol®

TO: Record

Attachment 4 of the sponsor's submission of November 2, 1994, requesting a meeting with the Division, consists of a record of a telephone conversation. This record appears to be, in part, a compilation of several conversations. In several general dialogues, the sponsor requested that I provide information on the product, Obetrol. I was informed that the NDA had been purchased from Rexar Pharmacal by Richwood Pharmaceuticals. The history of the product is vague and I was unable to locate any information on the product other than a personal file maintained by previous CSOs and a reference in COMIS. As a follow-up to our October 19, 1994, telephone conversation, Mr. Demos requested that I provide any information that I had available. In my letter of October 26, 1994, I provided a copy of the deficiency letter of September 9, 1980, and a Federal Register notice, dated September 25, 1973.

My comments, documented in Mr. Demos' record of conversation of June 20, 1994, are basically accurate; however, several caveats were omitted.

Points 4 & 5: The framework of this portion of the discussion was in reference to DESI products in general, not specifically Obetrol. I explained that over several decades, unresolved DESI issues could be counted in the 100's; however, as of today, only a few issues are still unresolved and this product could be a case in point.

Point 6, 8 & 11: I asked Mr. Demos if the NY District was requesting any actions on his part and explained that based on my limited personal file, I was unaware of any requirements placed on him by this Division other than those mentioned in the letter of September 9, 1980. He explained that he also had very limited records for the product. The context of this statement was such that due to both our limited documentation, the appropriate step at this time would be to make no changes and to attempt to locate the NDA file through the FOI office. I explained that I was unable to complete an administrative history on his product, in that I had no documents to review and could not advise him at this time. I explained that the NDA file appeared to have been retired.

Point 7: I informed Mr. Demos that COMIS lists his product as "Approved 19 JAN 60". I went on to explain that COMIS is merely a computer database utilized to track documents and was one of the tools that I would utilize to reconstruct the administrative history of his product.

attachment

Post-it™ Fax Note 7671 | Date 6/20/94 | # of pages ▸ 1
To Roger Griggs | From Thad Demos
Co. | Co.
Phone # | Phone #
Fax # | Fax #

FAXED

TO: Roger Griggs

FROM: Thad Demos

DATE: June 20, 1994

I called the Division of Neuropharmacology at FDA 301-594-2850. I spoke with Steve Hardeman via telephone.

RE: Obetrol Analytical Procedure #1000. The following are comments made by Steve Hardeman:

1. It appears there was a supplement submitted in the mid 1970's that was never approved.

2. There were numerous conversations between Rexar and the FDA regarding the procedure.

3. Rexar was permitted to market the product pending resolution.

4. He believes that this issue was never followed through by the FDA.

5. He stated there were hundreds of issues like this on other products that "fell through the cracks" in the 1970's.

6. He said to continue marketing the product using the current analytical procedure (procedure 1000).

7. Obetrol is listed in the FDA computer as an approved drug using the current formulation.

8. He said we do not have to do anything at this point.

9. He said that it may take some time for the Division of Neuropharmacology to find all of their records on this analytical issue "if at all".

10. He said "If we need a speedy resolution we should withdraw the supplement and then resubmit it to the Agency".

11. He said "we may continue to market the product with No Interruptions" using our current Analytical Method (#1000).

DIV FILE

MINUTES OF MEETING
Commercial Sponsor - Richwood Pharmaceuticals
NDA 11-522 / IND

DRUG:	Obetrol/Adderall
SPONSOR:	Richwood Pharmaceuticals
INDICATION:	ADHD - Narcolepsy - Exogenous Obesity
DATE/TIME:	January 19, 1995 : 0900-1045 hrs
LOCATION:	Woodmont II / 6th Floor Conference Room G

ATTENDEES:

FDA

Robert Temple, M.D.	CDER/ODEI
Paul Leber, M.D.	CDER/DNDP
Thomas Laughren, M.D.	CDER/DNDP
Andrew Mosholder, M.D.	CDER/DNDP
Stanley Blum, Ph.D.	CDER/DNDP
John Purvis, SCSO	CDER/DNDP
Steve Hardeman, CSO	CDER/DNDP
Stephanie Gray	CDER/OC
Frank Fazzari	CDER/OC
Charma Konnor	CDER/OC
Bradford Williams	CDER/OC
Patrick Savino	CDER/EXEC SEC
Sherry Danese	CDER/DDMAC
Eric Blumberg	OGC

RICHWOOD PHARMACEUTICALS

Roger Griggs	President, Richwood Pharmaceuticals
Robert Martz, M.D.	International and Domestic Consulting Services
Robert Hunt, M.D.	Center for Attention & Hyperactivity Disorders
Ronald Jones, M.D.	Chairman of Pediatrics, Orem Community Hospital
Martha Bennett	Bennett and Associates
Jess Stribling	King & Spalding

BACKGROUND:

Approval of NDA 11-522, a combination of amphetamine and methamphetamine, was withdrawn by the Commissioner's order effective on October 5, 1973. Notice of the ruling was published in the Federal Register of September 25, 1973, "Final Order on Certain Combination Anorectic Drugs".

The Division of Neuropharmacological Drug Products notified the Office of Compliance in February 1982, that the product was unapproved, but no further action was taken. In February 1994, Richwood Pharmaceuticals purchased Rexar Pharmacal and began distributing Obetrol products as Adderall.

In May 1994, during a routine inspection of Richwood Pharmaceuticals (formerly Rexar), significant current good manufacturing (CGMP) violations, including inadequate manufacturing process and test method validation, stability data problems, and record keeping deficiencies were found. These violations were listed in a FD-483 (a list of inspectional observations) left with Richwood, and were summarized in a warning letter sent to the company in June 1994. Richwood's response to FDA's observations was deemed unsatisfactory, and Richwood was notified of the agency's evaluation by letter dated August 23, 1994. FDA's New York District Office has been working with Richwood in an effort to get the company back into compliance with CGMP. During a September 1994 meeting with the New York District Office, Richwood committed to effect, by March 1995, CGMP corrections relating to Adderall. In December 1994, FDA conducted a limited inspection of Richwood and found additional CGMP violations. Despite all of the foregoing, to date FDA has not initiated any compliance action against the company.

PURPOSE:

Following receipt of the "Warning Letter", Mr. Jess H. Stribling, Attorney for Richwood Pharmaceuticals, requested a meeting with the agency to 1) discuss the medical necessity of Adderall and 2) the sponsor's request to continue marketing the product pending completion of the application. He claimed that the product is medically necessary for a segment of ADHD patients who have insufficient response to, no response to, or significant side effects from methylphenidate, pemoline, or dextroamphetamine. The Division of Neuropharmacology, responding to a consultation request from the Office of Compliance, determined that there was no credible evidence that Adderall was different from ordinary dextroamphetamine and that the drug was not a medical necessity. The sponsor was informed of the Division's determination on December 15, 1994, by Laurence Daurio, Compliance Officer, New York District, FDA. Subsequently, the agency agreed to meet with the sponsor to discuss Adderall and the company's plans for the product.

DISCUSSION:

The agency convened the meeting with introductions and several precursory statements. The sponsor was advised that 1) Adderall is an unapproved new drug, 2) that the Adderall promotional campaign had been false and misleading, and 3) we were present to listen, but would not decide on action at this meeting.

Mr. Griggs presented a brief history of Richwood Pharmaceuticals and the purchase of Rexar Pharmacal. He stated that Rexar had represented that the NDA was approved but conceded that Richwood's due diligence process was inadequate. During the due diligence process, he discovered that Obetrol was being prescribed primarily for the treatment of Attention Deficit Disorder with Hyperactivity (ADHD) but that sales were minimal. He indicated that the product initially represented wholesale sales of only and that they had considered dropping it from the product line. Based on some physician's testimony as to special benefit in a segment of ADHD patients, he decided not to drop Obetrol, and instead, to promote it. The current market for Adderall is

Mr. Stribling acknowledged that, as a matter of law, the product is an unapproved new drug. He further stated that the product is not listed in the Orange Book (Approved Drug Products). However, since the firm was in receipt of an agency form letter referring to Obetrol as an approved new drug (Information Request "Dunner" Letter), the sponsor concluded that their product was approved. He stated that the product, as reformulated, has been marketed since 1973, and requested that the sponsor be allowed to continue marketing the product pending the submission of the appropriate chemistry and manufacturing controls supplement and the correction of several GMP deficiencies.

Following queries from the agency, the sponsor stated that there is no evidence, based on adequate and well controlled clinical trials, that would allow the inference that Adderall is different or better than any other single entity amphetamine product in the treatment of ADHD or narcolepsy. They stated that they initiated a study that addressed their question on March 1, 1994, but it was not complete. The agency informed the sponsor that clinical studies must be conducted under an IND.
The sponsor agreed that their promotions and advertising were excessive and indicated that they had not consulted the advertising regulations prior to initiating the Adderall promotional campaign. They stated that their campaign was based solely on patient and physician testimony and stated that they were no longer seeking a determination that Adderall is a medical necessity.

SUMMARY:

1. The sponsor acknowledged that their advertising campaign had been misleading, and if allowed to continue to market Obetrol, agree to corrective advertising.

2. The sponsor agreed to submit an appropriate chemistry supplement to NDA 11-522. The firm did not commit to a specific date for such a submission, but agreed to contact the agency with a proposed date.

3. The sponsor agreed to correct their GMP deficiencies and to coordinate with the New York District to specify the date for such corrections.

4. The sponsor agreed that if they were allowed to market Obetrol and then should fail to submit an appropriate chemistry supplement and correct their GMP deficiencies by the agreed upon dates, they would cease marketing the product.

5. The sponsor agreed to open an IND to conduct clinical studies.

Steven D. Hardeman, R.Ph.
Consumer Safety Officer
DNDP

cc:
ORIG NDA 11-522
ORIG IND
HFD-120/Div File
HFD-100/Temple
HFD-120/Leber
/Laughren/Mosholder
/Blum
/Purvis
/Hardeman
HFD-244/Rose/Danese
HFD-300/Gray/Williams/Konnor
GCF-1/Blumberg

C:\DOCS\IND4\ADDERALL\47301\Adderall.mm1

Draft: 1/26/95, 2/2/95
Final: 2/22/95

MEETING MINUTES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 11-522/S-011, S-015

Richwood Pharmaceutical Company Inc.
Attention: Robert Falconer
7900 Tanners Gate Drive
Florence, KY 41042

JUL 17 1997

Dear Mr. Falconer:

Please refer to your supplemental new drug applications S-011 and S-015 for Adderall® 10mg and 20 mg Tablets.

These supplemental applications provide for the following labeling changes:

1. S-011 removes the obesity indication, includes a report of congenital anomalies under the Pregnancy/Teratogenic Effects section, and provides for some minor editorial changes.

2. S-015 removes the statement "Warning: May be habit forming" from the labeling attached to the exterior of the bottles.

We have completed our review of supplemental applications S-011 and S-015 and they are approved.

Labeling changes of this kind are permitted by section 314.70(c) of the regulations, and may be established prior to approval of the supplement. We note that these changes have been effected.

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 Melina Malandrucco, R.Ph., Project Manager, at (301) 594-5526.

Sincerely yours,

/S/ 7/17/97

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

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 11-522
HFD-120/Div. files
HFD-120/CSO/Malandrucco /S/ 7/14/97
HFD-120/Leber/Laughren/Mosholder/Blum/Scarpetti /S/ 7/16/97
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)

/S/ 7-17-97

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

Division of Neuropharmacological Drug Products

JUL 16 1997

PROJECT MANAGER REVIEW

Application Number: NDA 11-522/S-011, S-015

Name of Drug: ADDERALL® Tablets

Sponsor: Richwood Pharmaceutical Company *Inc*

Materials Reviewed:
Last Approved Labeling S-010- February 29, 1996

Supplement 011- July 24, 1996 (Identified as MG 10185 Revised May 1996)

Supplement 015- December 31, 1996 (Identified as MF 2060 Revised Aug 1996)

Review and Evaluation:
SLR-011: See enclosed document which highlights changes to the last approved labeling using "stikeouts" and "additions" markings. Additionally, CSO review comments are included which identify the type of labeling change. In a line by line comparison between the last approved labeling (S-010) and the proposed labeling only those changes indicated by the sponsor were made.

SLR-015: These changes were only made to the printing of the labeling attached to the exterior of the Adderall® 10 and 20 mg bottles. The statement "Warning: May be habit forming" has been deleted.

All changes within SLR-011 and SLR-015 were submitted as "Changes Being Effected".

Summary of Labeling Revisions (See enclosed document for specific changes):
There are 15 labeling revisions identified in the enclosed document.

Labeling changes 1,3,4,11, and 12 are deletions in various sections related to the removal of the obesity indication.
Labeling changes 5,6,9,10, and 15 are editorial changes.
Labeling changes 7 and 8 are changes to the Pregnancy Teratogenic Effects section.
Labeling change 2 is the renaming of the Actions section.
Labeling changes 13 and 14 are changes to the HOW SUPPLIED section.

Recommendation:
These indicated revisions have been approved by the medical and chemistry reviewers. I recommend approval of SLR-011 and SLR-015.

/S/

Melina Malandrucco, Project Manager

/S/ 7/16/97

Jack Purvis, Chief Project Management Staff

4 Page(s) Redacted

DRAFT LABELING

DEPARTMENT OF HEALTH & HUMAN SERVICES 81 Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JAN 15 1997
NDA No. 11-522

Richwood Pharmaceutical Company
7900 Tanner's Gate Drive-Suite 200
Florence, KY,41042

Attention: Robert A. Falconer

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ADDERALL-TABLETS

NDA Number: 11-522

Supplement Number: S-015

Date of Supplement: December 31, 1996

Date of Receipt: January 10, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 11, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

/S/

(FOR) John Purvis

Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FORM FDA 3217b (11/95)

★ U.S. GPO: 1995-404-697/20714

DUPLICATE

Richwood Pharmaceutical Company, Inc.

☐ CORPORATE HEADQUARTERS
7900 TANNERS GATE DRIVE
SUITE 200
FLORENCE, KY 41042
800-536-7878

☐ MANUFACTURING DIVISION
396 ROCKAWAY AVENUE
VALLEY STREAM, NY 11581
516-561-7662
516-561-7665 (FAX)
800-561-7661

December 31, 1996

NDA NO. 11-522 SLR-015

NDA SUPPL FOR EPL

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

Refer to CSO for Labeling Review 6/11/97 /S/

RE: CHANGES BEING EFFECTED for Adderall ® Tablets
Approved Supplemental NDA 11-522

Dear Dr. Leber:

Enclosed are twelve (12) of the final printed labeling for Adderall ® (dextroamphetamine saccharate, dextroamphetamine sulfate, amphetamine aspartate, and amphetamine sulfate) 10mg and 20 mg tablets with the "Warning: May be habit forming" statement deleted. These revised labels went into effect on 12/17/96.

Sincerely,

M. Madigan for Robert Falconer

RICHWOOD PHARMACEUTICAL CO., INC.
Robert A. Falconer
Corporate Director,
Regulatory & Technical Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 10 1997
HFD-120

DEPARTMENT OF HEALTH & HUMAN SERVICES 7.1 Public Health Service

Food and Drug Administration
Rockville MD 20857

Date AUG 12 1996

NDA No. 11-522

Richwood Pharmaceutical Company
7900 Tanner's Gate Drive- Suite 200
Florence, KY 41042

Attention: Robert A. Falconer

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ADDERALL-TABLETS

NDA Number: 11-522

Supplement Number: S-011

Date of Supplement: July 24, 1996

Date of Receipt: July 30, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 29, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

/S/

Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FORM FDA 3217b (11/95)

★ U.S. GPO: 1996-404-697/20714

Richwood Pharmaceutical Company, Inc.

☐ CORPORATE HEADQUARTERS
7900 TANNERS GATE DRIVE
SUITE 200
FLORENCE, KY 41042
800-536-7878

☐ MANUFACTURING DIVISION
396 ROCKAWAY AVENUE
VALLEY STREAM, NY 11581
516-561-7662
516-561-7665 (FAX)
800-561-7661

ORIGINAL
NDA SUPPLEMENT

NDA NO. 11-552 REF. NO. SLR-011

July 24, 1996

NDA SUPPL. FOR Labeling

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

RE: CHANGES BEING EFFECTED for Adderall ® Tablets
Approved Supplemental NDA 11-522

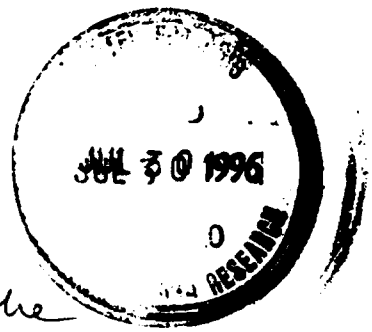
Dear Dr. Leber:

As requested in your letter dated April 9, 1996 enclosed are sixteen (16) of the final printed labeling for Adderall ® (dextroamphetamine saccharate, dextroamphetamine sulfate, amphetamine aspartate, and amphetamine sulfate) 10 mg and 20 mg tablets. Also enclosed, is a highlighted copy of the package insert changes. This revised package insert went into effect on 7/22/96.

Sincerely,

RICHWOOD PHARMACEUTICAL CO., INC.

Robert A. Falconer
Corporate Director,
Regulatory & Technical Affairs



9/12/96 These changes remove the obesity indication, include a report of congenital anomaly under the Pregnancy/Teratogenic Effects heading, and provide for some minor editorial changes. The revised labeling is acceptable

/S/
Medical Officer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 11-522/S-017

Richwood Pharmaceutical Company Inc.
Attention: Robert Falconer
7900 Tanners Gate Drive
Florence, KY 41042

JUL 25 1997

Dear Mr. Falconer:

Please refer to your supplemental new drug application S-017 for Adderall® 10mg and 20 mg Tablets.

This supplemental application provides for the following labeling changes:

APPEARS THIS WAY
ON ORIGINAL

1. The first sentence in the WARNINGS section reading "When tolerance...be discontinued." has been deleted.

2. The word "antiobesity" in the DRUG INTERACTIONS section has been replaced with the word "anorectic" under the Lithium Carbonate subsection.

3. The word "Amphetamine" in the CARCINOGENESIS/MUTAGENESIS section was written in lowercase instead of being capitalized.

4. In the HOW SUPPLIED section a toll-free number "1-800-536-7878" has been added for information and assistance.

We have completed our review of supplemental application S-017 and it is approved.

Labeling changes of this kind are permitted by section 314.70(c) of the regulations, and may be established prior to approval of the supplement. We note that these changes have been effected.

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 Melina Malandrucco, R.Ph., Project Manager, at (301) 594-5526.

Sincerely yours,

/S/ 7/24/97

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 11-522
HFD-120/Div. files
HFD-120/CSO/Malandrucco /S/ 7-22-97 /S/ 7/23/97
HFD-120/Leber/Laughren/Mosholder /S/ 7-24-97
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

ADDERALL®
TABLETS

Ⓒ

JUL 25 1997

BSD
SLR-017

Labeling: Original
NDA No: 11-522 Rc'd. 6-25-97
Reviewed by: [illegible]

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AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

DESCRIPTION: A single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate.

EACH TABLET CONTAINS:	10 mg	20 mg
Dextroamphetamine Saccharate	2.5 mg	5 mg
Amphetamine Aspartate	2.5 mg	5 mg
Dextroamphetamine Sulfate USP	2.5 mg	5 mg
Amphetamine Sulfate USP	2.5 mg	5 mg
Total amphetamine base equivalence	6.3 mg	12.6 mg

Inactive Ingredients: sucrose, lactose, corn starch, acacia and magnesium stearate.

Colors: ADDERALL 10 mg contains FD & C Blue #1
ADDERALL 20 mg contains FD & C Yellow #6 as a color additive

CLINICAL PHARMACOLOGY: Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

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

INDICATIONS: Attention Deficit Disorder with Hyper-

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Deficit Disorder with Hyperactivity: Adderall is indicated 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 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. Nontocalizing (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.

In Narcolepsy

CONTRAINDICATIONS:
Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.
Agitated states.
Patients with a history of drug abuse.
During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS: Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Usage in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

PRECAUTIONS: General: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension.

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions: *Acidifying agents* - Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines.
Urinary acidifying agents - (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.
Adrenergic blockers - Adrenergic blockers are inhibited by amphetamines.
Alkalinizing agents - Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.
Antidepressants, tricyclic - Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
MAO inhibitors - MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause [illegible] and other signs of

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and efficacy of amphetamines.

Adrenergic blockers -
Adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents -
Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Antidepressants, tricyclic -
Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors -
MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines -
Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives -
Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine -
Chlorpromazine blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide -
Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol -
Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate -
The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine -
Amphetamines potentiate the analgesic effect of meperidine.

Methenamine therapy -
Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

Norepinephrine -
Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital -
Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin -
Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene -
In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids -
Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions:

- Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.
- Amphetamines may interfere with urinary steroid determinations.

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Carcinogenesis/Mutagenesis: Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed.

Pregnancy - Teratogenic Effects: Pregnancy Category C. Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal stenosis (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Pediatric Use: Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

Amphetamines have been reported to exacerbate 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 Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines 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. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

ADVERSE REACTIONS:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphonia, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE:

Dextroamphetamine sulfate is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from

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Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE: Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal.

In rats, the oral LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg.

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis.

Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse.

Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine (Regitine®, CIBA) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

DOSAGE AND ADMINISTRATION: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

Attention Deficit Disorder with Hyperactivity: Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

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

Narcolepsy: Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

How Supplied

because of the resulting insomnia.

Attention Deficit Disorder with Hyperactivity: Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

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HOW SUPPLIED:

ADDERALL® 10 mg: Blue double-scored tablet, debossed "AD" on one side and "10" on the other side (NDC 58521-032-01)

ADDERALL® 20 mg: Orange double-scored tablet, debossed "AD" on one side and "20" on the other side (NDC 58521-033-01)

In bottles of 100 tablets.

Dispense in a tight, light-resistant container as defined in the U.S.P.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Richwood Pharmaceutical Company Inc.
Florence, KY 41042
1-800 536-7878

MG #10185
Revised: May 1997

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JUL 23 1997

Division of Neuropharmacological Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 11-522
Name of Drug: Adderall® 10 mg and 20 mg Tablets
Sponsor: Richwood Pharmaceutical Company, Inc
7900 Tanners Gate Drive
Florence, KY 41042

Material Reviewed

Submission Date(s): July 17, 1997 (SLR-011) - Last approved labeling
June 24, 1997 (SLR-017) - MG #10185 Revised May 1997

Background and Summary Description: Supplement 017 was submitted as a "Changes Being Effected".

Review

1. Supplement 017 includes the following changes to the package insert:

   a. The first sentence in the WARNINGS section reading "When tolerance...be discontinued." has been deleted.

   b. The word "antiobesity" in the DRUG INTERACTIONS section has been replaced with the word "anorectic" under the Lithium Carbonate subsection.

   c. The word "Amphetamine" in the CARCINOGENESIS/MUTAGENESIS section was written in lowercase instead of being capitalized.

   d. In the HOW SUPPLIED section a toll-free number "1-800-536-7878" has been added for information and assistance.

All the above changes are acceptable to the medical reviewer.

Conclusions

In a line by line comparison of the last approved supplement SLR-011 and the proposed labeling, no changes other than those specified by the sponsor were made. I recommend approval.

/S/

Project Manager

Supervisory Comment/Concurrence:

/ST 7/23/97

Supervisor, Project Management Staff

cc:

Original
HFD-120/Div. Files
HFD-120/Malandrucco

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JUL 8 1997

NDA No. 11-522

Richwood Pharmaceutical Company Inc.
7900 Tanners Gate Drive
Suite 200
Florence, KY. 41042

Attention: Robert A. Falconer

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Adderall Tablets

NDA Number: 11-522

Supplement Number: S-017

Date of Supplement: June 24, 1997

Date of Receipt: June 25, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 24, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours, /S/

(For) John Purvis

Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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ORIGINAL

Richwood Pharmaceutical Company, Inc.

CENTER FOR DRUG
REC'D
JUN 25 1997
HFD-120
EVALUATION AND RESEARCH

June 24, 1997

Dr. Paul Leber, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Woodmont II, Document Room
HFD-120
1451 Rockville Pike
Rockville, MD 20852

(SS)
...A 11522 REF. NO. SLR-017
...SUPPL FOR Labeling

RE: Special Supplement - Changes Being Effected
ADDERALL® Tablets 10 mg and 20 mg
NDA 11522
Package Insert revised 5/97

Dear Dr. Leber:

Pursuant to 21 CFR 314.70, Richwood Pharmaceutical Company Inc. is submitting the following changes to the ADDERALL® package insert:

1. Deleted the first sentence in the WARNINGS section:

When tolerance to the anorectic effect develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued.

Justification for change in the labeling:

> This sentence was removed because ADDERALL is not indicated for the treatment of obesity or for an anorectic effect.

2. Changed the wording associated with Lithium Carbonate under Drug Interactions section:

The word "antiobesity" was replaced with the word "anorectic". The statement now reads as follows: *"Lithium carbonate* - The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate."

7/7/97 These changes are acceptable
/S/
Medical Officer

7900 Tanners Gate • Suite 200 • Florence, Kentucky 41042 • Phone (606) 282-2100 • Fax (606) 282-2103

Justification for change in the labeling:

> ADDERALL is not indicated for the treatment of obesity. Therefore, the proper description of the pharmacologic effect is the use of the adjective "anorectic" instead of suggestion of an indication which is implied by the term "antiobesity."

3. In the Carcinogenesis/Mutagenesis section, the word "Amphetamine" should not be capitalized; so it was changed to read "amphetamine".

4. In the How Supplied section a toll-free company telephone number "1-800-536-7878" has been included to assist persons who need to contact the company to obtain information about ADDERALL®.

The revised package insert is identified as Revision 5/97 and was included with packaged drug product beginning on June 11, 1997.

Twelve (12) copies of revised package insert are enclosed with this supplemental submission.

If you have any questions concerning this submission, please call the undersigned at (606) 282-2100.

Sincerely,
Richwood Pharmaceutical Company Inc.

Jon W. Banning

Jon W. Banning, Ph.D.
Manager, Regulatory & Technical Affairs

enclosure

MAR 16 1998

NDA 11-522/S-019

Richwood Pharmaceutical Company, Inc.
Attn: Robert Falconer
7900 Tanners Gate Drive
Suite 200
Florence, KY 41042

Dear Mr. Falconer:

Please refer to your supplemental new drug application dated October 24, 1997, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetics Act for Adderall® Tablets.

The User Fee goal date for this application is April 27, 1998.

The supplemental application provides for:

The supplement was submitted as "Special Supplement - Changes Being Effected".

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

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 Ms. Melina Malandrucco, Regulatory Project Management Officer, at (301) 594-2850.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

/S/

Maryla Guzewska, Ph.D.
Chemistry Team Leader, DNDC-1
Division of Neuropharmacological Drug Products
(HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA 11-522
HFD-120/Div. Files
HFD-120/CSO/MMalandrucco
HFD-120/MGuzewski /S/ 3.14.98
HFD-110/RMittal
HFD-810/CHoiberg
HFD-92/DDM-DIAB
HFR-MA300/NWJ-D

APPROVAL (AP)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

MAR 14 1998

NDA #: 11-522/S-019 **REVIEW DATE:** 13-MAR-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT SCS-019	24-OCT-97	27-OCT-97	18-FEB-98

SUPPLEMENT PROVIDES FOR

Special Supplement Changes being Effected

The use of revised in-process controls for tableting Adderall 30 mg Tablets.

NAME & ADDRESS OF APPLICANT

Shire Richwood Inc.
7900 Tanners Gate, Suite 200
Florence, kentucky 41042

DRUG PRODUCT NAME

Proprietary: ADDERALL
Nonproprietary/USAN: Amphetamine Salts

PHARMACOL.CATEGORY/INDICATION: **Attention Deficit Disorder and Narcolepsy**

DOSAGE FORM: Tablets
STRENGTHS: 5 mg, 10 mg, 20 mg and 30 mg

ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

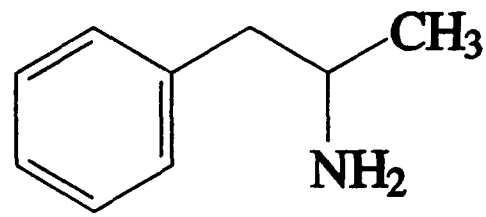
CHEMICAL NAME
Drug Substance I - (+)-α-Methylphenethylamine sulfate
Drug Substance II - (±)-α-Methylphenethylamine asparate
Drug Substance III - (+)-α-Methylphenethylamine saccharate
Drug Substance VI - (±)-α-Methylphenethylamine sulfate

CAS # 300-62-9 (Amphetamine)

MOLECULAR FORMULA $C_9H_{13}N$ (Amphetamine)

MOLECULAR WEIGHT 135.21 (Amphetamine)

STRUCTURAL FORMULA (Amphetamine)



Amphetamine

SUPPORTING DOCUMENTS:

None.

RELATED DOCUMENTS (if applicable):

CONSULTS: None

REMARKS/COMMENTS:

In support of the the applicant provided following:

- A copy of the revised current Adderall 30 mg Tablets, Master Production Batch Record dated 9/22/97.
- A representative copy of the executed batch Adderall 30 mg Tablets, which was one of the process validation batches using the revised Master Production Batch Record.
- A copy of the Field Copy Certification statement.

CONCLUSIONS & RECOMMENDATIONS:

Approval is recommended.

APPEARS THIS WAY
ON ORIGINAL

cc:
original NDA
HFD-120/Division File
HFD-92
DISTRICT OFFICE
HFD-110/Ram Mittal
HFD-120/CSO
R/D Init by:M. Guzewska 3.14.98

/S/

/S/

Ramsharan D. Mittal Ph.D., Review Chemist
filename:C:\NDA\11522\11522.019

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

9.1

Date OCT 30 1997

NDA No. 11-522

Shire Richwood Inc.
7900 Tanners Gate Drive
Florence, KY 41042

Attention: Rober A. Falconer

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Adderall Tablets

NDA Number: 11-522

Supplement Number: S-019

Date of Supplement: October 24, 1997

Date of Receipt: October 27, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 26, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

/S/

(For) John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FORM FDA 3217b (11/95)

★ U.S. GPO: 1996-404-897/20714

Shire Richwood Inc.

ORIGINAL

Friday, October 24, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

OCT 27 1997

RECEIVED HFD-120

Dr. Paul Leber, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Woodmont II, Document Room
HFD-120
1451 Rockville Pike
Rockville, MD 20852

RE: Adderall® Tablets, 30 mg 11-522 - Supplemental Applications
Changes Being Effected – Revised In-Process Controls

11-522 SUPPL. NO. SCS-019
ORIGINAL FOR Controls

Dear Dr. Leber:

This supplemental application is to provide for the use of revised
Reference is also made to our supplemental new drug application S-013, approved on 5/12/97, which provided copies of the original master batch compression record for Adderall Tablets 30 mg. The changes being effected with this supplement went into effect for regular production on 10/22/97

Attachment A is a copy of the revised current Adderall® 30 mg Tablets Master Production Batch Record dated 9/22/97.

Attachment B is a representative copy of the executed batch B4267 Adderall® 30 mg Tablets, which was one of the process validation batches using the revised Master Production Batch Record.

Attachment C is a copy of the Field Copy Certification statement.

7900 Tanners Gate • Suite 200 • Florence, Kentucky 41042 • Phone (606) 282-2100 • Fax (606) 282-2103

Please contact the undersigned at (606) 282-2100 extension 2143, or Nicholas LaLima, Technical Director in New York at (516) 561-7662, if you need any further information to complete your review for this supplement

Sincerely,

SHIRE RICHWOOD INC.

Robert A. Falconer
Senior Director,
Technical Affairs

APPEARS THIS WAY
ON ORIGINAL