CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 016618/S041

Trade Name: PONDIMIN TABLETS

Generic Name: FENFLURAMINE HYDROCHLORIDE

Sponsor: WYETH-AYERST LABORATORIES

Approval Date: 08/29/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 016618/S041

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 016618/S041

APPROVAL LETTER

NDA 16-618/S-041

AUG 29 1997

Wyeth-Ayerst Laboratories
Attention: Joseph Sonk, Ph.D.
Senior Director, Women's Health Care Products
U.S. Drug Regulatory Affairs
PO Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Sonk:

We acknowledge your August 28, 1997 supplemental new drug application received on August 29, 1997 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pondimin (fenfluramine hydrochloride) Tablets.

We also acknowledge your correspondence dated July 17 and 24 and August 15, 1997

The supplemental application provides for revised warning language that is to be incorporated in a black box for valvular heart disease and primary pulmonary hypertension (PPH) for the physician labeling. In addition, a statement regarding the lack of information concerning the safety and effectiveness of the combined use of fenfluramine and phentermine is included in the black box. Also, included is a statement that fenfluramine is approved only as a single agent for short term use.

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 in the draft labeling in the submission dated August 28, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on August 29, 1997.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. 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 16-618/S-041. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become

available, 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.

If you have any questions, please contact:

Maureen Hess, MPH, RD
Consumer Safety Officer
(301) 827-6411

Sincerely yours,

8-29-97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 16-618
HFD-510/Div. files
HFD-510/GTroendle/LLutwak/BStadel/EColman/MHess
HFD-102/L.Ripper
HFD-101/L.Carter
HFD-820/Yuan Yuan Chiu
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

APPEARS THIS WAY
ON ORIGINAL

drafted: Mhess/August 29, 1997/n16618s41.ap

r/d Initials:
final:

APPROVAL

APPEARS THIS WAY
ON ORIGINAL

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 016618/S041

MEDICAL REVIEW(S)

ORIGINAL

AUG 29 1997

MEDICAL OFFICER'S REVIEW OF NDA LABEL SUPPLEMENT

NDA NO. 16-618; CORRESPONDENCE
GENERIC NAME: FENFLURAMINE HYDROCHLORIDE
TRADE NAME: PONDIMIN
SPONSOR: WYETH-AYERST LABORATORIES
P.O. Box 8299
Philadelphia, PA 19101-8299
Tel: (610) 902-3740
FAX: (610) 964-5973
ATTN: Joseph S. Sonk

DATE SUBMITTED: 08/27/97
DATE REC'D, CDER: 08/28/97
DATE RECEIVED, M.O.: 08/28/97
DATE REVIEWED, M.O.: 08/28/97

The Sponsor has submitted a revised patient package insert, based on revised labeling, including "black box" warnings concerning cardiac valvulopathy and pulmonary hypertension.

The material is being reviewed based on a FAX copy submitted; the actual material and diskette have been received at time of this review. The following comments should be submitted to the Sponsor.

Page 1, Section "What important information should I know about PONDIMIN?", lines 1-8:
Since these lines contain the material in the black box of the label, they should be bolded and/or enclosed in a black box.

Page 1, Section "What important information should I know..."; line 2:
"...patients taking Pondimin and other appetite suppressants." This should be changed to to simply omit from "the other" to end of line.
"...patients taking Pondimin."

Page 1, Section "What important information..."; line 4:
After "...Adipex-P®", add: **"However, the valvular disease has also been reported in patients taking Pondimin alone."**

Page 1, Section "What important information..."; line 6:
"...an often fatal disorder." This should be changed to reflect the wording in the "black box" to "...a **frequently** fatal disorder."

Page 2, Section "What other important information..."; lines 1-5:
Suggested changes are acceptable.

Page 4, Section "How long should I take PONDIMIN?"; line 1:
Suggested change is acceptable.

Page 4, Section "What are the possible side effects..."; lines 3 and 7:
Suggested changes are acceptable.

Page 4, Section "What are the possible side effects...";
Recommend adding statements about PPH and valvular heart disease with reference back to page 1.

Leo Lutwak, M.D., Ph.D.
August 29, 1997

cc: NDA Arch.
HFD-510
HFD- 240
HFD-240/AReb/LPalmer
HFD-510/MHess/GTroendlel/LLutwak

8-29-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 016618/S041

CORRESPONDENCE

NDA NO. 16618 REF. NO. 041

NDA SUPPL FOR SLR

ORIGINAL

NDA SUPPLEMENT

WYETH-AYERST RESEARCH

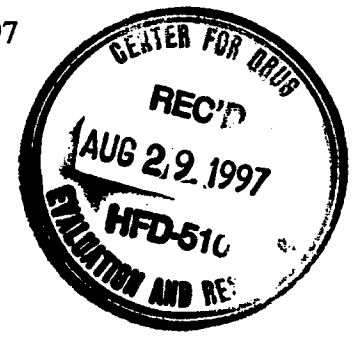
P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

NDA No. 16-618
Pondimin® Tablets

August 28, 1997



Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Room 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Special Supplement-Changes Being Effected.

Dear Dr. Sobel:

Reference is made to our approved New Drug Application No. 16-618 for Pondimin, (fenfluramine hydrochloride) Tablets.

Further reference is made to our submission of July 17, 1997 in which Wyeth-Ayerst provided the Agency with proposed language to be incorporated into a boxed warning for valvular heart disease and primary pulmonary hypertension (PPH) for physician labeling for Pondimin Tablets. Reference is also made to the Agency's letter dated August 13, 1997 that provided FDA's language for the boxed warning and requests that this change be made and submitted to the Agency as final printed labeling no later than two weeks after receipt of FDA's letter. Reference is made to our August 15, 1997 submission in which we provided alternate wording for the above-referenced boxed warning. Finally, reference is made to our discussions of August 27, 1997 in which Wyeth-Ayerst and FDA agreed on final language for the boxed warning for physician labeling.

While Wyeth-Ayerst has agreed to implement the wording requested by FDA, we do wish to note our disagreement on the boxed warning language pertaining to PPH, specifically

the omission of the following underlined text:

> "Primary pulmonary hypertension-a rare, frequently fatal disease of the lungs-has been found to occur with increased frequency in patients receiving appetite suppressants, including fenfluramine. (See WARNINGS)."

We feel the omission of this text is not supported by available data, including the International Primary Pulmonary Hypertension Study (IPPHS)
. It is our understanding that the IPPHS found no obvious difference between classes of anorexigens, only that some were more used than others, and therefore, the underlined text more accurately reflects the IPPHS data.

This submission will confirm that the Agency has not requested the implementation of labeling to contraindicate the concomitant use of fenfluramine with phentermine or other appetite suppressants.

The purpose of this submission is to provide 20 copies of final printed labeling (FPL) as requested in the Agency's August 27, 1997 letter that incorporates the box warning into the currently approved Pondimin labeling (CI 4676-4, April 9, 1997), as finalized in the above-referenced telephone conference. In support of this Special Supplement-Changes Being Effected, enclosed are the following attachments

1) 20 Copies of final printed labeling (10 mounted; one highlighted for the reviewer's convenience) which incorporates the boxed warning text.
2) A copy of the currently approved Pondimin physician labeling.

Wyeth-Ayerst has made every effort to meet the Agency's deadline for submission and implementation of final printed labeling containing the boxed warning. Accordingly, this labeling will be implemented immediately.

Should you have any questions regarding this information, please call the undersigned at (610) 902-3772 or Mr. Robert Quinty at (610) 902-3789.

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO
9-8-97
CSO INITIALS DATE

Sincerely,
WYETH-AYERST LABORATORIES

Joseph S. Sonk, Ph.D., Senior Director
Women's Health Care Products
U.S. Drug Regulatory Affairs

RHQ:\pondpbox