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**Application Number: NDA 18891/S015**

## APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-891/S-015
S-016

SEP 6 1996

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Dawn Watson, R.Ph.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Watson:

Please refer to your February 17 (S-015) and November 7 (S-016), 1995 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Catapres-TTS (clonidine hydrochloride) Transdermal Therapeutic System.

We acknowledge receipt of your amendments to both applications dated June 18 and August 6, 1996.

The supplemental applications provide for:

S-015

Draft labeling extensively revised (as described in enclosure #2 to our May 30, 1996 approvable letter) under **DESCRIPTION, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE,** and **DOSAGE AND ADMINISTRATION.**

S-016

Draft labeling revised under **PRECAUTIONS** and **WARNINGS:**

The **PRECAUTIONS: Withdrawal** subsection was moved to the **WARNINGS** section and revised to read as follows:

> **WARNINGS Withdrawal** Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and confusion accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. The likelihood of such reactions to discontinuation of clonidine therapy appears to be greater after administration of higher doses or continuation of concomitant beta-blocker treatment and special caution is therefore advised in these situations. Rare instances of

hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal. When discontinuing therapy with Catapres, the physician should reduce the dose gradually over 2 to 4 days to avoid withdrawal symptomatology.

An excessive rise in blood pressure following discontinuation of Catapres therapy can be reversed by administration of oral clonidine hydrochloride or by intravenous phentolamine. If therapy is to be discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blocker should be withdrawn several days before the gradual discontinuation of Catapres.

The **PRECAUTIONS: Pediatric Use** subsection was revised to read as follows:

**Pediatric Use** Safety and effectiveness in pediatric patients below the age of twelve have not been established (See Warnings on Withdrawal).

We have completed the review of these supplemental applications including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling.

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 NDAs 18-891/S-015 and S-016. Approval of this submission by FDA is not required before the labeling is used.

We note that you have already printed a 3-month supply of labeling in which you did not delete the bold sentence at the end of the **WARNINGS Withdrawal** subsection as indicated in our marked-up draft. This labeling may be distributed until the time of your next printing.

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.

under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

/S/ 9/2/96 3pm 8/6/96

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HF-2/MedWatch (with draft/final labeling)
HFD-80 (with draft/final labeling)
HFD-110
HFD-110/Project Manager
HFD-110/Reviewers and Team Leaders
HFD-40 (with draft/final labeling)
HFD-613 (with draft/final labeling)
HFD-735 (with draft/final labeling)
DISTRICT OFFICE
HFD-222/New Drug Chemistry Division Director
HFD-110/DRoeder
sb/8/20/96

9.3.96

Approval Date: September 3, 1974

APPROVAL