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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-727

Approvable Letter (s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

G. Buehler

NDA 20-727

JUL 2 1997

Medco Research, Inc.
Attention: Janice L. Parry, Pharm.D.
P.O. Box 13886
Research Triangle Park, NC 27709

Dear Dr. Parry:

Please refer to your July 3, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BiDil (hydralazine HCl and isosorbide dinitrate) 37.5/10, 37.5/20, 75/20, and 75/40 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated August 2, 9, 12 and 13, September 12 and 26, October 24, November 20, 21 and 26, December 11, 12, 13 and 18, 1996; January 2 (two), 9, 13, 23 (two), 27 (two) and 31, February 3 (two), 12 and 24 (two) and April 14, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

MEDICAL

The Cardiovascular and Renal Drugs Advisory Committee did not recommend approval of the combination of isosorbide dinitrate and hydralazine for the treatment of congestive heart failure. The Division of Cardio-Renal Drug Products and I concur with that recommendation.

The only support for approval is the mortality results of VHeFT I. There were fewer deaths in the combination treated population than there were in the placebo treated or prazosin treated populations. The p values for this difference (adjusted for multiple comparisons, multiple testing, interim analysis, etc.) vary from 0.019 to 0.11 (2-sided) depending on the analysis method, the imputation method utilized for missing covariants and overall vs. 2-year survival. Although the combination did not detect a symptomatic benefit (e.g., exercise tolerance, hospitalizations for congestive heart failure, hospitalizations for any reason, and either the patient or physician quality of life responses), a survival advantage would be a basis for approval. The results of VHeFT 1, however, are not convincing enough to support approval alone, particularly in light of the results of VHeFT II.

The other study conducted that could possibly offer confirmation of the VHeFT I mortality finding is VHeFT II. Unfortunately, VHeFT II was not placebo-controlled and the combination treatment was statistically significantly inferior to enalapril with respect

to 2-year mortality. Using a cross-study comparison of BiDil in VHeFT-II with the placebo in VHeFT-I, you have suggested that even though enalapril was superior to BiDil, BiDil in VHeFT-II could still be superior to no treatment. To conclude that BiDil is effective, one must believe that enalapril was more than 30% better on 2-year survival than the combination (VHeFT II) and that the combination in turn was more than 30% better than a placebo (had there been one) (i.e., the VHeFT I effect). That would require an overall effect (vs placebo) of enalapril of more than 50%, a far greater effect of enalapril than has been seen in symptomatic patients of any NYHA class. Indeed, the difference between enalapril and the combination in VHeFT II is greater (32% reduction at 2 years) than the difference between enalapril and placebo in the SOLVD treatment study (23% at 2 years).

CHEMISTRY

1. We still do not believe that you have adequately addressed the possibility of an interaction between the drug substances to form N-nitrosoamines, products that have the potential to be carcinogenic.

   Please test tablets from several of your oldest batches for the presence of nitrosoamines to determine if these compounds are present, and if so, at what concentration.

2. Please provide the thermal stress studies data obtained by gradient HPLC. The data should indicate a mass balance of the amounts of the decomposed and related substances with the active ingredients of BiDil tablets.

3. Based on the analytical results, the NDA method appears not to be suitable for regulatory control of the product. One extra large peak was found in method [ ] that was not identified and the [ ] for the compound are significantly different from the one shown in the method. We also note that the product did not meet your specifications for impurities of NMT [ ] Impurity amounts in the four lots tested were [ ] and [ ]. Please clarify.

In addition, we have the following comments and requests for information that should be addressed:

PHARMACOKINETICS

1. In view of the fact that the 37.5/10 mg tablet showed a slower dissolution performance compared to the 37.5/20, 75/20 and 75/40 in all 4 media tested, an in-vivo bioavailability waiver cannot be granted for the two middle strengths (37.5/20, 75/20). However, the multiple-dose study that you are currently conducting using all strengths in CHF patients could provide the necessary data.

2. When asked to provide the pharmacokinetic parameters for study CB02 in electronic form on diskette the only data submitted was for the normalized parameters to a weight of 65 kg. Upon review, it was discovered that the data on diskette did not match the data found in the NDA, and the discrepancy remains unexplained. In future submissions, please validate all data sets before they are submitted.

3. Your proposal for inclusion of information regarding food-effect on hydralazine and isosorbide dinitrate based on published literature cannot be accepted. A food-effect study, using the to-be-marketed formulation of BiDil, will be required to support any statement relating to the effect of food on administration of BiDil.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
Telephone: (301) 594-5332

Sincerely yours,

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

cc:
Original NDA
HFD-2/MLumpkin
~~HFD-110~~
HFD-110/Project Manager
HFD-92
HFD-101
DISTRICT OFFICE
HFD-810/New Drug Chemistry Division Director
HFD-110/GBuehler;4/18/97
sb/3/5/97;3/27/97;4/4/97;4/16/97;4/18/97;7/2/97
R/D RLipicky;4/18/97
ADeFelice/4/10/97;4/18/97
JAdvani/4/6/97
JShort for RWolters/4/4/97
PMarroum/4/4/97;6/18/97
CGanley/4/9/97;4/18/97;7/1/97
SChen/4/4/97;7/1/97;7/2/97
JHung/4/4/97;7/1/97
EBelair/4/10/97
NMorgenstern/4/15/97;4/17/97;4/18/97;7/1/97
RWolters/4/18/97;7/1/97

NOT APPROVABLE