

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-151

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Z McMichael

Food and Drug Administration
Rockville MD 20857

JAN 24 2000

NDA 21-151

Berlex Laboratories
Attention: Ms. Maria Garrigan
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-2000

Dear Ms. Garrigan:

Please refer to your new drug application dated June 18, 1998, received June 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Betapace (*d,l*-sotalol) 80, 120, 160 and 240 mg Tablets.

We acknowledge receipt of your submissions dated June 24, September 18 and November 12, 1998; January 26, February 9, March 22, 23 and 25, April 1 (two), 9, 15, 22 and 27, May 11 and 19, July 8, 16 (two), and 22, August 23, September 7, 16, 20 and 28, and October 1 and 26, 1999.

This application provides for the new indication of prolongation of time to recurrence of symptomatic AFIB/AFL in patients with symptomatic AFIB/AFL, with or without structural heart disease but in the absence of uncompensated congestive heart failure.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be essentially identical in content to the enclosed draft and should include, in addition, a patient package insert modeled on the enclosed patient labeling recently approved for dofetilide. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy showing the changes that have been made.

Please also provide a detailed proposed plan for educating physicians about how to use sotalol in the treatment of atrial arrhythmias (need for hospitalization, dose adjustment based on creatinine clearance and QT, etc.) and assuring that physicians prescribing sotalol have had appropriate training. We realize that the availability of other dosage forms of sotalol may make attempts to limit distribution of sotalol for AF difficult.

We have considered your proposed use of the name Betapace AF. We appreciate the advantage of separate labeling for a *d,l*-sotalol product intended to treat atrial arrhythmias, as the guidance for physicians and patients is quite different from that associated with use in treatment of

ventricular arrhythmias, and separate labeling will permit focused educational efforts. On the other hand, we do not believe it is impossible to label a single product for both uses. Given the potential availability of generic products, which, three years after approval of your application, will be able to include an AF claim, in addition to a ventricular arrhythmia claim, and given the ability of physicians to prescribe using the generic term sotalol, it seems inevitable that some patients to be treated with *d,l*-sotalol for atrial arrhythmias will receive products other than the proposed Betapace AF. Although there is no perfect solution to this problem, we suggest two possible approaches:

1. Continue to call *d,l*-sotalol products Betapace. Develop a PPI that explains the two different uses of *d,l*-sotalol and gives advice appropriate to the AF use, along with unit of use packaging. Generic products, when they are approved, could not utilize this claim or have a PPI referring to it until your 3 year exclusivity has ended. At that time, generic products would need a PPI, unit of use packaging and an appropriate education program.
2. Utilize the Betapace AF name during the period of exclusivity for the AF claim, a period that can be used for education and training of physicians. After that period, recognizing that generic products could be approved with both claims (and a PPI, unit of use packaging, and an appropriate education program), Berlex could continue with separate products or switch to a single product.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. 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.

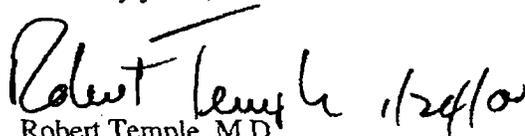
Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Cardio-Renal Drug Products to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this application.

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Sincerely yours,


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

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cc:

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HFD-110/Div. Files

HFD-110/Z.McDonald

HFD-002/ORM

HFD-101/ADRA

HFD-95/DDMS

HFD-40/DDMAC (with labeling)

DISTRICT OFFICE

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23 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ _____ § 552(b)(5) Draft Labeling

Withheld Track Number: Approval Ltrs- /