

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-151**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

ORIGINAL

**BERLEX**

UPS Overnight

February 29, 2000



Berlex Laboratories, Inc.

340 Changebridge Road  
P.O. Box 1000  
Montville, NJ 07045-1000  
Telephone: (973) 276-2000

Raymond Lipicky, MD, Director  
Division of Cardio-Renal Drug Products, HFD 110  
Center for Drug Evaluation & Research  
Food and Drug Administration  
1451 Rockville Pike  
Rockville, Maryland 20852

ORIG AMENDMENT  
(XR)

Re: NDA 21-151

**BETAPACE AF (Sotalol Hydrochloride)**

**AMENDMENT OF PATENT AND CLAIMED EXCLUSIVITY UPON APPROVAL**

Dear Dr. Lipicky:

Reference is made to NDA 21-151 for Betapace AF<sup>TM</sup> which was approved on February 22, 2000 for the maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm.

This submission amends the patent information contained in NDA 21-151, pursuant to 21 CFR 314.53(c)(2)(ii). Accordingly, this submission provides information pertaining to the patent that claims the composition and method of use for Betapace AF<sup>TM</sup> and a statement of claimed exclusivity for the product, as it was approved by FDA on February 22, 2000.

Two copies of this submission are being provided to the Division in accord with 21 CFR 314.53(d)(4), an Archival Copy and a Chemistry Section Review Copy.

A copy of this submission is being provided to the Data Base Management and Services Branch, so that the Approved Drug Products with Therapeutic Equivalence Evaluations ["Orange Book"] can be updated to reflect the information applicable to Betapace AF<sup>TM</sup> as approved February 22, 2000, in accord with 21 CFR 314.53(e). A copy of our letter to the Data Base Management and Services Branch, dated February 29, 2000, is enclosed in this submission under Item 19: Other.

ORIGINAL

NDA 21-151  
Betapace AF  
February 29, 2000  
Page 2 of 2

Please call me at (973) 276-2193 if you have any questions concerning this submission.

Sincerely,  
BERLEX LABORATORIES



Maria C. Garrigan  
Manager  
Drug Regulatory Affairs

betAF010.doc

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN  
ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338  
Expiration Date: April 30, 2000  
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT: Berlex Laboratories, Inc. DATE OF SUBMISSION: February 29, 2000

TELEPHONE NO. (Include Area Code): (973) 276-2193 FACSIMILE (FAX) Number (Include Area Code): (973) 276-2016

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 340 Changebridge Road, P.O. Box 1000, Montville, New Jersey 07450-1000  
AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE: N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-151

ESTABLISHED NAME (e.g., Proper name, USP/USAN name): Sotalol Hydrochloride PROPRIETARY NAME (trade name) IF ANY: Betapace AF<sup>TM</sup>

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any): N-[4-[1-hydroxy-2-[(methylethyl)amino]-ethyl]-phenyl]-methanesulfonamide monohydrochloride CODE NAME (If any): MJ-1999-1, MJ-5763-1

DOSAGE FORM: Tablet STRENGTHS: 80, 120, 160mg. ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL) in patients with symptomatic AFIB/AFL who are currently in sinus rhythm]

APPLICATION INFORMATION

APPLICATION TYPE:  New Drug Application (21 CFR 314.50)  Abbreviated Application (ANDA, AADA, 21 CFR 314.94)  Biologics License Application (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE:  505 (b) (1)  505 (b) (2)  507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION: Name of Drug: N/A Holder of Approved Application

TYPE OF SUBMISSION (check one):  ORIGINAL APPLICATION  AMENDMENT TO A PENDING APPLICATION  RESUBMISSION  PRESUBMISSION  ANNUAL REPORT  ESTABLISHMENT DESCRIPTION SUPPLEMENT  SUPAC SUPPLEMENT  EFFICACY SUPPLEMENT  LABELING SUPPLEMENT  CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT  OTHER

REASON FOR SUBMISSION: Amendment of Patent Information and Claimed Exclusivity Upon Approval

PROPOSED MARKETING STATUS (check one):  PRESCRIPTION PRODUCT (Pxx)  OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1 THIS APPLICATION IS:  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.  
Not applicable

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 19-865 - Betapace<sup>®</sup> IND 2,544 - oral d,l-sotalol HCl

ORIGINAL

This application contains the following items: (Check all that apply)		
	1. Index	
	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
	3. Summary (21 CFR 314.50 (c))	
	4. Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)	
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
x	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
x	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
	16. Debarment certification (FD&C Act 306 (k)(1))	
	17. Field copy certification (21 CFR 314.5 (k) (3))	
	18. User Fee Cover Sheet (Form FDA 3397)	
x	19. OTHER (Specify)	

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.**

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Maria C. Garrigan Manager Drug Regulatory Affairs	DATE February 29, 2000
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ADDRESS (Street, City, State, and ZIP Code) 340 Changebridge Road P.O. Box 1000 Montville, New Jersey 07450 - 1000	Telephone Number (973) 276 - 2193
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Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

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Please **DO NOT RETURN** this form to this address.

**BERLEX**  
Laboratories, Inc.

NDA 21-151  
Betapace AF™

**13. PATENT INFORMATION**

Pursuant to 21 CFR 314.50(h) and 21 CFR 314.53(d)(1), the undersigned declares that the United States patents listed below apply to sotalol, and that he is not aware of any other U.S. patents covering this drug substance.

Type of Patent	Patent Number	Issued	Expiration Status
Compound	3,341,584	September 12, 1967	Expired
Composition/ Method of Use	3,478,149	November 11, 1969	Expired

BERLEX LABORATORIES, INC.



Robert Chabora  
President, DD&T

2-29-00

Date

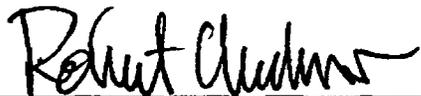
**BERLEX**  
Laboratories, Inc.

NDA 21-151  
Betapace AF™

**14. PATENT CERTIFICATION**

A patent certification with respect to patents which claim sotalol or a use of sotalol pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to this application.

BERLEX LABORATORIES, INC.



Robert Chabora  
President, DD&T

2-29-00

Date

**Statement of Claimed Exclusivity**

Pursuant to 21CFR 314.50(j) and with reference to 21CFR 314.108(b)(5), Berlex Laboratories, Inc. hereby submits this statement of claimed marketing exclusivity.

1. Berlex claims exclusivity under 21CFR 314.108(b)(4);
2. 21CFR 314.108(b)(4)(i – iv) support this claim;
3. Pursuant to 21CFR 314.50(j)(4), this application, NDA 21-151, contains new clinical investigations that were essential to approval of the indication for Betapace AF™, i.e., the maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. NDA 21-151 was approved on February 22, 2000. The new clinical investigations contained herein were conducted and sponsored by either Berlex Laboratories, Inc. or by Bristol-Myers Squibb (BMS) prior to the transfer of IND 2,544 for dl-Sotalol Hydrochloride (Oral) from BMS to Berlex on November 16, 1992.

**Certification of Claimed Exclusivity pursuant to 21 CFR 314.50(j)(4)(i), (ii) and (iii)**

This is to certify that to the best knowledge of Berlex Laboratories, Inc. ["Berlex"], that:

- (i) each of the clinical investigations included in this supplemental application meets the definition of "new clinical investigation" set forth in 314.108(a);
- (ii) Berlex has thoroughly searched the scientific literature of all published studies and publicly available reports of clinical investigations known to the applicant that are relevant to the maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm, the approved indication for Betapace AF™, and that in Berlex's opinion, such published studies and publicly available reports do not provide a sufficient basis for the approval of this indication, without reference to the new clinical investigations contained in this application, as these published studies and publicly available reports do not provide sufficient evidence of efficacy and safety. The published data either contained a mixed population of different supraventricular arrhythmias or lacked a double-blind placebo comparator. The Berlex study [Protocol 106-05] is the only study which provides dose-response data which is essential for approval.
- (iii) Berlex was the sponsor named in the Form FDA-1571 for IND 2,544 for dl-Sotalol Hydrochloride (Oral), under which Protocol 106-05, one of the new clinical investigations, which was essential to the approval of this application, was conducted. The remaining ten studies essential to the approval of this application were conducted by Bristol-Myers Squibb (BMS), and were completed either prior to or after IND 2,544 was transferred to Berlex on November 16, 1992.

UPS Overnight

**BERLEX**

February 29, 2000

Berlex Laboratories, Inc.

340 Changebridge Road  
P.O. Box 1000  
Montville, NJ 07045-1000  
Telephone: (973) 276-2000

Mary Ann Holovac, R.Ph.  
Data Base Management and Services Branch, HFD-93/NLRC  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

**Re: NDA 21-151 – Betapace AF™ (Sotalol HCl)**  
**AMENDMENT OF PATENT INFORMATION AND CLAIMED EXCLUSIVITY**  
**UPON APPROVAL**

Dear Ms. Holovac:

Reference is made to NDA 21-151 for Betapace AF™ which was approved on February 22, 2000 for the maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. Attachment 1 contains a copy of the approval letter.

The purpose of this submission is to request an update of the next supplement to the Approved Drug Products with Therapeutic Equivalence Evaluations ["Orange Book"] to reflect the information applicable to Betapace AF™ (NDA 21-151), in accord with 21 CFR 314.53(e). Berlex believes that a separate line listing for Betapace AF™ is warranted and the following background information regarding NDA 21-151 is provided.

NDA 21-151 was originally submitted as an efficacy supplement on June 18, 1998 to NDA 19-865 for Betapace® tablets. (NDA 19-865 was approved on October 30, 1992 for the prevention of life-threatening ventricular arrhythmias). However, during the preparation for the April 29, 1999 Cardio-Renal Drug Products Advisory Committee Meeting that reviewed the AFIB/AFL indication, we had several discussions with the Division of Cardio-Renal Drug Products concerning the benefits and risks associated with the use of d,l-sotalol for treating two different indications and patient populations. Specifically, the dosing regimen and safety information differ and require consideration for treating each indication differently. In addition, the Division requested that a patient package insert be made available for patients who are being treated for AFIB/AFL, so they are made aware of the risks and benefits associated with taking d,l-sotalol for this indication. (This information would also be included in the physician package insert). However, for patients who are prescribed d,l-sotalol for the treatment of life threatening ventricular arrhythmias, a patient package insert is not required.

In an effort to distinguish a product that will be used to treat two different indications, it was determined that this supplement be converted to a new NDA. This NDA provides a separate trade name, labeling, and package to assure that healthcare practitioners and AFIB/AFL patients receive the necessary dosing and safety information regarding the use of this product.

There are substantial differences in the labeling between Betapace AF™ and Betapace®. A side-by-side comparison of the physician package inserts for each product is provided in Attachment 2. The language that is different is highlighted in color (red for Betapace AF™ and blue for Betapace®) and the language that is common to both package inserts is in black. Below is a table which highlights the important differences between Betapace AF™ and Betapace®.

	<b>NDA 21-151 Betapace AF™</b>	<b>NDA 19-865 Betapace®</b>
<b>Indication</b>	The maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm	The treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician are life-threatening
<b>Labeling</b>	Physician Package Insert with a Black Box Warning <sup>a</sup>  Patient Package Insert	Physician Package Insert <sup>a</sup>  <u>NO</u> Patient Package Insert
<b>Available Doses</b>	80 mg, 120 mg, and 160 mg WHITE tablets	80 mg, 120 mg, 160 mg and 240 mg LIGHT BLUE tablets
<b>Packaging</b>	Unit of Use Packaging which consists of bottles of 60 tablets, Patient Package Insert attached	Bottles of 100 tablets, <u>NO</u> Patient Package Insert
<b>Education for Healthcare Practitioners</b>	An educational program required by FDA which includes: <ol style="list-style-type: none"> <li>1. Clear description of the limitations to the indications (i.e. only those patients who are highly symptomatic).</li> <li>2. Risks associated with Betapace AF™ (especially emphasizing that Betapace AF™ can cause serious ventricular arrhythmias).</li> <li>3. Information on how to minimize this risk (i.e., Betapace AF™ dosing and treatment initiation information).</li> </ol>	No educational program required

<sup>a</sup> Please see Attachment 2 for a side-by-side comparison of the physician package inserts for each product

With regard to the available doses, it is important to note that the 240 mg dose is not approved for Betapace AF™. The physician package insert for Betapace AF™ specifically states that doses greater than 160 mg BID have been associated with an increased incidence of torsade de pointes

(a potentially dangerous arrhythmia that can be caused by certain antiarrhythmic drugs) and are not recommended for the AFIB/AFL indication. However, for the treatment of a life-threatening condition such as that for which Betapace® is approved, a physician must judge whether this increased risk is acceptable.

With the background information regarding Betapace AF™ (NDA 21-151) and the important differences between the Betapace AF™ and Betapace® NDAs listed in the table above in mind, it is our understanding that Betapace AF™ will appear as a separate line listing in the Orange Book (see Attachment 3). Moreover, the approved package insert for Betapace AF™ specifically notes, in the Black Box Warning, that "Betapace® ...should not be substituted for Betapace AF™ because of significant differences in labeling (i.e., patient package insert, dosing, and safety information)". This cautionary language appears again in the Indications and Usage section as follows: Betapace® ...must not be substituted for Betapace AF™ because of significant differences in labeling (i.e., patient package insert, dosing, and safety information)".

Also, the Betapace AF™ package insert contains a section, entitled "Transfer to Betapace AF™ from Betapace®", which specifically addresses AFIB/AFL patients who are transferred to Betapace AF™ from Betapace®. This section states "Patients with a history of symptomatic AFIB/AFL who are currently receiving Betapace® for the maintenance of normal sinus rhythm should be transferred to Betapace AF™ because of significant differences in labeling (i.e., patient package insert, dosing, and safety information)".

A copy of the approved physician package insert for Betapace AF™ is provided as Attachment 4.

The patient package insert for Betapace AF™ provides AFIB/AFL patients with important information regarding the treatment of their condition with sotalol. In the section entitled "What is Betapace AF™?" the following wording can be found: "This information about Betapace AF™ was developed to ensure that you and your doctor get the right information about your type of irregular heartbeats. Consult your doctor before you accept any other sotalol product that does not include this patient information."

A copy of the Betapace AF™ patient package insert is provided as Attachment 5.

We believe these significant differences in the Betapace AF™ physician package insert and patient package insert warrant a line listing for Betapace AF™ that is separate from that for Betapace® in the Orange Book.

In addition, several sponsors of generic formulations of sotalol have obtained tentative approval for their ANDAs. The reference listed drug product, which these ANDAs are based upon, is Betapace® (NDA 19-865). It is our understanding that once the Orphan Drug Exclusivity for Betapace® (which had been extended an additional six months based upon the submission of pediatric data) expires on April 30, 2000, these generic formulations will be AB rated with Betapace® and not Betapace AF™. The generic formulations of sotalol will be approved only for the life-threatening ventricular arrhythmia indication and contain labeling identical to Betapace®. Betapace AF™ is entitled to three years of market exclusivity. In an environment where generic products for Betapace® will be available, a distinct and separate line listing for Betapace AF™ will provide a means for physicians to be better assured that the AFIB/AFL patients who are prescribed Betapace AF™ will be receiving the correct product and information appropriate for their condition.

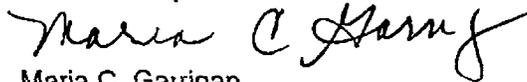
Data Base Management and Services Branch, HFD-93/NLRC  
NDA 21-151 – Betapace AF™  
February 29, 2000  
Page 4 of 4

Lastly, Attachment 6 provides, to the Data Base Management and Services Branch, a copy of our submission to the Division of Cardio-Renal Drug Products, dated February 29, 2000, which amends the patent information contained in NDA 21-151, pursuant to 21 CFR 314.53(c)(2)(ii). That submission also includes a statement of claimed exclusivity for Betapace AF™ in accordance with 21 CFR 314.108.

We would appreciate your confirmation that it is appropriate for Betapace AF™ to have a separate line listing in the Orange Book.

Please call me at (973) 276-2193 if you have any questions concerning this submission.

Sincerely,  
BERLEX LABORATORIES



Maria C. Garrigan  
Manager  
Drug Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # 21-151  
~~19-865~~ SUPPL # ~~007~~

Trade Name Betapace AF Generic Name Sotalol HCl

Applicant Name Berley Laboratories HFD # 110

Approval Date If Known February 22, 2000

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?  
YES /\_\_\_/ NO /\_\_\_/

b) Is it an effectiveness supplement?  
YES // NO /\_\_\_/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES // NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES // NO /\_\_\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /\_\_\_/ NO //

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/      NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /

If yes, explain: \_\_\_\_\_

\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /  / NO /

4. If yes, explain: \_\_\_\_\_

\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study # 05

Study # 001f

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1                      YES /\_\_\_/                      NO /  /

Investigation #2                      YES /\_\_\_/                      NO /  /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_  
\_\_\_\_\_

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /  /

Investigation #2                      YES /\_\_\_/                      NO /  /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

\_\_\_\_\_  
\_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

      # 05                            \_\_\_\_\_  
      # 004                            \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # 2,544 YES /  / ! NO / \_\_\_ / Explain: \_\_\_\_\_  
!  
! \_\_\_\_\_

Investigation #2 !  
IND # \_\_\_ YES /  / ! NO / \_\_\_ / Explain: \_\_\_\_\_

*Foreign* \_\_\_\_\_

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
YES / \_\_\_ / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_  
!  
! \_\_\_\_\_  
!  
! \_\_\_\_\_

Investigation #2 !  
YES / \_\_\_ / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_  
!  
! \_\_\_\_\_  
!  
! \_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /  / NO /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

Zeke McDonald  
Signature  
Title: \_\_\_\_\_

6/4/99  
Date

R. M. Smith for RSL  
Signature of Division Director

6/8/99  
Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

**PEDIATRIC PAGE**

(Complete for all original applications and all efficacy supplements)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at time of the last action.**

NDA/BLA # 21-151-19-865 Supplement # 007 Circle one:  SE1 SE2 SE3 SE4 SE5 SE6

HF          Trade and generic names/dosage form: Betapace (Sotalol HCl) Tablets Action: AP AE NA

Applicant Berlex Laboratories Inc Therapeutic Class 65

Indication(s) previously approved Documented ventricular arrhythmias such as sustained ventricular tachycardia

Pediatric information in labeling of approved indication(s) is adequate          inadequate         

Indication proposed in this application Prevention of 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.

**FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.**  
**IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?**          Yes (Continue with questions)          No (Sign and return the form)

**IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED?** (Check all that apply)

         Neonates (Birth-1month)          Infants (1month-2yrs)          Children (2-12yrs)          Adolescents(12-16yrs)

- 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
  - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
  - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
  - c. The applicant has committed to doing such studies as will be required.
    - (1) Studies are ongoing,
    - (2) Protocols were submitted and approved.
    - (3) Protocols were submitted and are under review.
    - (4) If no protocol has been submitted, attach memo describing status of discussions.
  - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

**ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER?**          Yes  No  
**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.**

This page was completed based on information from          (e.g., medical review, medical officer, team leader) Pediatric Written Request sent to Berlex on Jan. 15, 1999 - they are studying all antiarrhythmic indications.  
*Wanda Henderson, RHPM* 6/4/99  
Signature of Preparer and Title Date

cc: Orig NDA/BLA # 21-151-19-865-007 21-151  
HFD-110 /Div File  
NDA/BLA Action Package  
HFD-008/KRoberts - Crescena

(revised 10/20/97)

**FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)**

UPS Overnight

**BERLEX**

February 22, 2000

**Berlex Laboratories, Inc.**

340 Changebridge Road  
P.O. Box 1000  
Montville, NJ 07045-1000  
Telephone: (973) 276-2000

Raymond Lipicky, MD, Director  
Division of Cardio-Renal Drug Products, HFD 110  
Center for Drug Evaluation & Research  
Food and Drug Administration  
1451 Rockville Pike  
Rockville, Maryland 20852

**Re: NDA 21-151**  
**BETAPACE AF (Sotalol Hydrochloride)**  
**DEBARMENT CERTIFICATION STATEMENT**

Dear Dr. Lipicky:

This submission provides a revised debarment certification statement for NDA 21-151, as was requested in a telephone conversation with Mr. David Roeder, RHPM on February 22, 2000. This statement has been revised in accordance with the Draft Guidance for Industry, Submitting Debarment Certification Statements.

Please call me at (973) 276-2193 if you have any questions concerning this submission.

Sincerely,  
BERLEX LABORATORIES



Maria C. Garrigan  
Manager  
Drug Regulatory Affairs

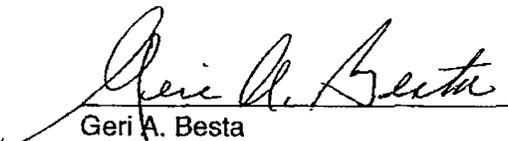
**BERLEX**  
Laboratories, Inc.

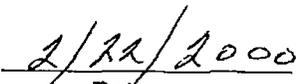
Betapace® (sotalol HCl) Tablets  
NDA 21-151

**Certification Under Section 306(k)(1) of the FD & C Act**

Berlex Laboratories, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 21-151 for Betapace® (sotalol HCl) Tablets.

BERLEX LABORATORIES, INC.

  
Geri A. Besta  
Manager, Regulatory Submissions &  
Information

  
Date

ENTERED INTO DFS on 4/21/00

Meeting Minutes

Z. McDonald

FEB 1 2000

Meeting Date: February 1, 2000  
NDA# 21-151 Betapace AF (sotalol) Tablets  
Sponsor: Berlex  
Document Date: January 28, 2000  
Type of Meeting: To discuss Berlex's proposed physician education program and specific points of the package insert.  
Classification: C (Guidance)

Meeting Chair: Robert Temple, M.D.  
Meeting Recorder: Zelda McDonald  
External Participant Lead: June Bray

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Robert Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Janet Norden	Consumer Safety Officer, DDMAC, HFD-42
Zelda McDonald	RHPM, HFD-110

Berlex:

June Bray	Director, Drug Regulatory Affairs
Maria Garrigan	Manager, Drug Regulatory Affairs
Wolfgang Kehr, M.D., Ph.D.	Vice President & General Manager, Therapeutics
Pran Marrott, M.D., M.Sc.	Director, Clinical Cardiovascular Research
Klaus Marten	Director of Marketing Therapeutics
Joseph Posluszny, Ph.D.	Director, Project Management, Cardiovascular
John Williams, M.D.	Senior Assoc. Medical Director, Clin. Cardiovascular Research

**Background**

The NDA for sotalol was approved on October 30, 1992 for "the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgment of the physician, are life-threatening." At the time of approval, Bristol-Myers Squibb (BMS) owned the NDA. BMS subsequently transferred the NDA to Berlex. On June 22, 1998, Berlex submitted an efficacy supplement for sotalol with the indication 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." The efficacy supplement was subsequently converted to a type 6 NDA. An approvable letter issued on January 24, 2000 for the 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 and requested that Berlex make revisions to the package insert. The letter also requested that Berlex provide a detailed proposed plan for educating physicians about how to use sotalol in the treatment of atrial arrhythmias and assuring that physicians prescribing sotalol have had appropriate training. Berlex requested this meeting to discuss their proposal for a Physician Education Program and to discuss/clarify changes to the package insert.

## Meeting

### PHYSICIAN EDUCATION PROGRAM

Berlex gave an overview (slides attached) of the anti-arrhythmic market and their continuing educational programs that included symposia, teleconferences, hospital/evening symposia and conventions (ACC/AHA/NASPE). Berlex proposed a tiered approach for their BetapaceAF Physician Education Program (see slides) that included a Dear Dr. letter and a BetapaceAF Treatment Kit. Berlex asked if their approach was acceptable and if the letter could state that FDA wanted physicians to know the importance of initial patient hospitalization and how to dose the patient.

- 



- 

- 



- The Agency agreed to help with the drafting of the Dear Dr. letter.

### MARKETING OPTIONS



- The Agency agreed.

### PACKAGE INSERT

The Agency generally considered Berlex's proposals reasonable but planned to consider them all more closely. Particular concern was noted about unexplained differences from dofetilide (e.g., differences in what QT should lead to discontinuation).

1. Berlex stated that the approvable letter requested that the Dosage and Administration section be made identical to that of Dofetilide, including diagrams, except where it is clearly not appropriate. Berlex proposed to start at a low dose (80 mg) and titrate up to 160 mg (see slides). This is distinct from the first mentioned dofetilide dosing regimen, which starts at a high dose and is titrated down, although the "start low" regimen is also given.
  - The Agency agreed that this approach is acceptable, but was concerned that the 160 mg dose was getting close to the dose that causes torsade with no real evidence of added benefit. Berlex proposed including the sentence, "The best effect is at 120 mg, 160 mg may be considered, but in the largest trial, there was no benefit from this dose." The Agency agreed with this general idea but would consider the exact wording.

2. The Agency agreed with Berlex's proposed wording for the Dosage and Administration/Maintenance of BetapaceAF therapy.
3. In the Dofetilide Dosage and Administration section, there is an introduction consisting of five bullets. Berlex asked if they could omit the last two bullets because that wording did not pertain to the situation with sotalol. The Agency agreed and also agreed to Berlex's proposed rewording of the first three bullets.
4. The Agency agreed with Berlex's proposal for the Black Box wording, but stated that Berlex would need to justify with data any differences between the sotalol wording and that of dofetilide, e.g., sotalol's Black Box has a minimum of 2 days in hospital versus dofetilide's 3 days.

TIMELINES

1. Berlex noted that the exclusivity for sotalol expires May 1, 2000 and asked for a quick turn around once they submit the revised labeling. They contended that their educational efforts would be of little value once generic products were available.
  - Without addressing that issue, the Agency said that the labeling revisions needed could be determined quickly.
2. Berlex asked if they had to provide the entire education program in detail before approval.
  - The Agency said Berlex should put in writing what they outlined in this meeting, including revisions based on our discussions. It would not have to be extremely detailed but should convey the important elements of the discussion.
3. The Agency agreed that the application could be approved on draft labeling.

Signature minutes preparer: Bella McDonald 2/8/00

Concurrence, Chair: Robert Kemp

Orig. NDA  
HFD-110  
HFD-111/McDonald  
HFD-111/Blount/Matthews

Drafted 2/3/00    Finald 2/7/00  
RD:  
Temple            2/7/00  
Fenichel         2/4/00  
Gordon           2/4/00  
Norden           2/4/00

31 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 1

FEB 22 2000

## RHPM Approval Overview

Application: NDA 21-151  
Betapace AF (*d,l*-sotalol)

Applicant: Berlex Laboratories

Approvable Letter: January 24, 2000

## Background

When the approvable letter was issued for NDA 21-151, the following issues were outstanding:

- The firm had to submit final printed labeling identical in content to the enclosed marked-up draft.
- The firm had to submit a proposal for an educational program.
- The firm could choose to market the drug as either Betapace or Betapace AF.

## Labeling

The firm submitted revised draft labeling in a submission dated February 7, 2000. A marked-up version of that draft was faxed to the firm on February 16, 2000. The sponsor submitted revised draft labeling dated February 17, 2000. The revised draft labeling incorporated all changes recommended in the fax of February 16 as well as a few minor changes that were agreed to over several telephone exchanges with me. Several minor exceptions were pointed out in their cover letter. Dr Temple commented on those changes, and the draft to be sent to the firm incorporates all of Dr. Temple's comments on these changes. The application will be approved on draft labeling.

## Nomenclature

The firm has decided to market this product as Betapace AF.

## Educational Program

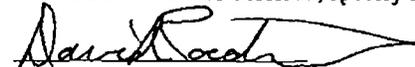
The firm submitted a proposed educational program along with the labeling in a submission dated February 7, 2000. DDMAC provided comments on the educational program that were sent to the sponsor. The sponsor agreed in their submission of February 17, 2000 to incorporate those comments into their program. This will be confirmed in the approval letter.

## Pediatric Rule

The requirement for pediatric studies will be deferred for two years.

## Recommended Action

- Approve the NDA on draft labeling.
- Firm should revise key elements in educational program; specify in letter.
- Pediatric studies deferred; specify in letter.



David Roeder  
Regulatory Health Project Manager

cc: NDA 21-151  
HFD-110  
HFD-110/ZMcDonald



NOV 23 1999

Food and Drug Administration  
Rockville MD 20857

NOV 23 1999

Dr. Bengt Ullman  
Cardiology Department  
Södersjukhuset SE-118 83  
Stockholm, Sweden

Dear Dr. Ullman:

Between July 26 and 30, 1999, Drs. Antoine El-Hage and Khin Maung U and Ms. Nancy N. Mundo, representing the Food and Drug Administration (FDA), met with your sub-investigator, Dr. Inger Meijer-Carlsson, to review your conduct of a clinical study (Protocol No. CV 102-004/96053) of the investigational drug Betapace® (*d,l*-sotalol HCl) performed for Berlex Laboratories, Inc. This inspection is a part of the Agency's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

We have evaluated the inspection report and the documents submitted with that report. We note that at the close of the inspection, our personnel presented and discussed with your sub-investigator, Dr. \_\_\_\_\_ a list of their inspectional observations (Form FDA 483). The discussion included, but was not limited to, protocol deviations, missing informed consent documents and inadequate record keeping. We acknowledge Dr. \_\_\_\_\_ response to the items listed in Form FDA 483 in which she agreed to the observations.

We understand that your study was not conducted under a U.S. Investigational Drug Application (IND) and was thus not subject to our regulations. For future reference, we offer our comments in the same manner as we would had the study been performed in the U.S. We wish to emphasize the following:

1) Protocol Deviations

Two study subjects (#7044 and #2901) received prohibited concomitant medications, atenolol and digoxin, respectively, throughout their participation.

2) Records unavailable for the following:

The progress notes for 3 subjects (#7043, #7068 #7045) were missing, and therefore, case report form (CRF) entries could not be verified.

CC:

HFA-224

HFD-110 / Document Room: NDA 19-865/NDA 21-151  
HFD-110 / Review Division Div. Director: Dr. Ray Lipicky, M.D.  
HFD-110 / MO - Abraham Karkowsky, M.D., Ph.D.  
HFD-110 / RHPM / CSO - Zelda McDonald  
HFD-45 / Division File  
HFD-45 / Reading File  
HFD-47 / Chron File  
HFD-47 / U  
HFD-47 / Storms  
HFD-47 / GCP II File  
HFR-CE750 / DIB (DEMPSTER)  
HFR-CE750 / BIMO MONITOR (ROBINSON)  
HFR-CE7555/ FIELD INVESTIGATOR (MUNDO)  
HFC-134 / International Operations (KADAR)

CEN: \_\_\_\_\_

CIB (GCP II): \_\_\_\_\_

Field Classification: VAI

H.Q. Classification:

_____	1) NAI	
_____	2) VAI	- no response requested
_____	3) VAI-R	- response requested
<u>  X  </u>	4) VAI-RR	- response received
_____	5) OAI	

If the Field and Headquarters classifications are different, reasons for change in classification, if applicable:

Deficiencies Noted:

<u>  X  </u>	inadequate consent form
<u>  X  </u>	inadequate drug accountability
<u>  X  </u>	deviations from protocol
<u>  X  </u>	inaccurate and inadequate records
_____	failure to report ADR's
<u>  X  </u>	other: missing source documents

O: \ (uk \ ullman.doc)

drafted: KMU/ 10/21/1999

reviewed: AEH/ 10/25/1999

revised: KMU/ 10/28/1999

reviewed: AEH/ 11/18/1999

finalized: NLP/ 11/19/1999

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE SENT:** November 2, 1999

**DUE DATE:** N/A

**OPDRA CONSULT #:** 99-025

**TO (Division):**

Raymond Lipicky, MD  
Director, Division of Cardio-Renal Drug Products  
HFD-110

**PRODUCT NAME:** Betapace AF

**MANUFACTURER:** Berlex Laboratories

**NDA #:** 21-151

**CASE REPORT NUMBER(S):** Not applicable.

**SUMMARY:**

The Division of Cardio-Renal Drug products requested the review of the proposed proprietary name Betapace AF.

**OPDRA RECOMMENDATION:**

OPDRA objects to the use of the proprietary name Betapace AF.

*Jerry Phillips* 11/2/99  
Jerry Phillips  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3246  
Fax: (301) 827-5189

*Peter Honig*  
Peter Honig, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration  
*(as per previous discussions  
c HFD 110  
and OOE-1)*

Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm 15B03  
Center for Drug Evaluation and Research

MEDICATION ERROR REVIEW

**DATE OF REVIEW:** August 25, 1999  
**NDA#** 21-151  
**NAME OF DRUG:** Betapace AF (Sotalol Hydrochloride) Tablets  
**NDA HOLDER:** Berlex Laboratories

**I. INTRODUCTION:**

The Division of Cardio-Renal Drug Products (HFD-110) requested the evaluation of the proprietary name Betapace AF, manufactured by Berlex Laboratories.

Betapace AF (Sotalol Hydrochloride Tablets) is an antiarrhythmic drug with Class II (beta-adrenoreceptor blocking) and Class III (cardiac action potential duration prolongation) properties. Betapace AF has both beta-adrenoreceptor blocking and cardiac action potential duration prolongation antiarrhythmic properties. After oral administration, peak plasma concentrations are reached in 2.5 to 4 hours, and steady-state plasma concentrations are attained within 2 to 3 days. Distribution occurs to a central and to a peripheral compartment, with a mean elimination half-life of 12 hours. Excretion is predominantly via the kidney in the unchanged form and lower doses are necessary in conditions of renal impairment. Betapace AF is indicated for prolonging the time to recurrence of symptomatic AFIB/AFL in patients with a history of symptomatic AFIB/AFL, without structural heart disease or with structural heart disease in the absence of uncompensated heart failure. It is also indicated for the treatment of documented life-threatening ventricular arrhythmias.

OPDRA inquired why Betapace AF was the subject of a new NDA and not a supplement for a new indication under NDA 19-685 as is the common regulatory process within CDER. The project manager stated that this application was filed as a supplement but was changed to a separate NDA for public health reasons. The reasons being that if approved it will be for the new indication and be marketed as unit-of-use bottles with a patient package insert. The sponsor's exclusivity with respect to sotalol, will expire in October of 1999 and generic manufacturers will be able to market their formulations for use in life-threatening ventricular arrhythmias but only Betapace AF will be permitted to market sotalol for the new indication. Generic manufacturers would not be permitted to promote the AF indication and would not have special warnings that might be necessary to the safe use of the drug in the AF population in their labeling even though their product would be freely substitutable at pharmacies. The division hoped that the public health would benefit from the distribution of AF-specific labeling.

Betapace (Sotalol Hydrochloride) was approved October 30, 1992 and is currently marketed under NDA 19-685, also manufactured by Berlex Laboratories.

Betapace has Orphan Drug Exclusivity (ODE), which expires October 30, 1999, for the treatment and prevention of life-threatening ventricular tachyarrhythmias.

Betapace is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician are life threatening.

Betapace contains the same **active** ingredient as Betapace AF, Sotalol Hydrochloride. In addition, it contains the same **inactive** ingredients as Betapace AF except for the dye utilized for the tablet color. Betapace AF is a white capsule-shaped tablet and Betapace is a light-blue capsule shaped tablet utilizing FD&C blue color #2.

Betapace is supplied as 80 mg, 120 mg, 160 mg and 240 mg tablets in bottles of 100 and unit-dose containers of 100. Betapace AF will be supplied as 80 mg, 120 mg, 160 mg tablet in bottles of 60 and unit-dose containers of 100.

The Office of Generic Drugs has received 9 ANDA's for Sotalol Hydrochloride Tablets, 5 are pending review and 4 have been issued NA letters. Approval of these applications could occur on October 30, 1999.

## II. SAFETY AND RISK ASSESSMENT:

1. OPDRA objects to the use of the suffix "AF" in conjunction with the proprietary name "Betapace" for the following reasons:

⇒AF has been utilized as an abbreviation for "Anti-Fungal" in two over-the-counter (OTC) products containing clotrimazole and miconazole. The AF could be misinterpreted as Anti-Fungal and could present safety issues with the use of the product.

⇒AF is a common medical abbreviation for "acid-fast, afebrile, amniotic fluid, anterior fontanel, antifibrinogen, aortofemoral, ascitic fluid and atrial fibrillation". The Agency has always considered the use of coined abbreviations in conjunction with proprietary names objectionable since they can and have been misinterpreted.

⇒The Committee for Proprietary Medicinal Products (CPMP) operating under the European Agency for the Evaluation of Medicinal Product Human Medicines Evaluation Unit (EMA), have issued a draft guidance on the acceptability of tradenames for medicinal products processed through the centralized procedure. This guidance references "The tradename of a product should avoid qualification by letters" as a reason for non-acceptance of a proposed tradename. We also refer you to ASHP Guidelines on Preventing Medication Errors in Hospitals (Am J Hosp Pharm., Vol. 50 Feb 1993), Draft Guidance for Industry on Proprietary Drug Names (May 1999) and The CDER Labeling and Nomenclature Committee, Structure, Function, and Process (Drug Information Journal, Vol. 31, Nov 1997).

2. No handwriting or verbal studies were conducted within OPDRA, because the proprietary name Betapace (Sotalol Hydrochloride) is already approved and currently marketed under NDA 19-685, also manufactured by Berlex Laboratories.
3. OPDRA believes that the decision to create a new NDA for Betapace AF should be re-evaluated for the following reasons:
  - ⇒OPDRA does not believe that the creation of two separate package inserts will prohibit generic substitutions especially in settings where medications are prescribed by generic name. If a hospital formulary only carries a generic Betapace (sotalol hydrochloride) it will be dispensed in the place of Betapace AF because there is no difference between the bioequivalence profiles of Betapace and Betapace AF. The only setting where a substitution will not take place is if the physician specifies "No substitution allowed" on a prescription.

⇒The creation of another proprietary name for a new indication adds unnecessarily to the growing number of tradenames in the United States, thus creating additional safety concerns. OPDRA believes that having 2 tradenames by the same manufacturer, for the same bioequivalent drug product is misleading to health care professionals, in that it infers a different product.

### III. REGULATORY AND POLICY ASSESSMENT:

The following comments are normally outside the expertise of OPDRA. However, the Associate Director of OPDRA offers his opinion from his experience in the Office of Generic Drugs and the Agency:

An Interim Guidance on Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under the Prescription Drug User Fee Act of 1992, states that requests for approval of a new indication, or a modification of a previously approved indication, should each be submitted individually in a separate supplement to an approved original application. In addition, the firm has not changed the dosage form or route of administration. The color of the tablet color is the only modification that has been made. The change in color of a tablet, which is often done by manufacturers, is usually accompanied by a statement on the container label, usually not to exceed a period of 6 months, which says "New Color".

Agency precedence for a similar approval occurred with Zyban and Wellbutrin. In this particular case labeling for Zyban had no similarity to Wellbutrin. In a 1998 CDER policy meeting, the Center agreed that we would not encourage this in the future. The approval of a new NDA will have a negative impact on Agency and Industry resources.

There are 9 generic applications pending approval for Betapace and if one of these firms decides to market "Betapace AF" for the new indication, a new application would have to be submitted. A greater number of Agency manpower would be utilized in the review process of the new application rather than that utilized in the review of a supplement. The increased cost incurred by the company will be reflected in the pricing of the generic when it hits the market place.

Another potential problem may arise if generic firms decide not to pursue approval of a separate application for the AFIB/AFL indication of Betapace due to cost constraints. If generic firms decide not to market this indication then generic Betapace labeling would never contain the labeling information associated with AFIB/AFL. If this indication were approved as a supplement, at the end of the 3 year exclusivity, generic firms would be required to include the information relating to AFIB/AFL.

OPDRA has consulted with OGD (Don Hare) and believes that because the labeling of Betapace AF has overlapping indications with Betapace it can NOT be given a therapeutic code of — (not equivalent).

If Betapace AF was submitted as a supplement for a new indication, the information relating to the new indication would get 3 years Waxman-Hatch exclusivity. Generic firms would not be able to include any information in the labeling of the product nor advertise this use until the expiration of the exclusivity. The only information that may be pertinent to public health safety is the proposed language in the patient package insert, which could be provided by supplying the Betapace AF.

There are several examples of NDA applications that have been granted exclusivity for a specific indication and as a result generic firms were requested to delete this indication from their labeling. Examples include the following:



- ⇒ Hytrin – Awarded exclusivity for Benign Prostatic Hypertension. The BPH indication had separate labeling that included a patient package insert, similar to the proposed Betapace AF. Generic firms were required to delete all information pertaining to BPH until the exclusivity expired.
- ⇒ Digoxin – This Pre 38 drug submitted an NDA for this product and was awarded exclusivity for the indication of Congestive Heart Failure. As a result all generic firms were requested to delete this indication from their labeling leaving only the indication for Afib.
- ⇒ Tiazac – Awarded exclusivity for the indication of the Management of Chronic Stable Angina. This indication would be required to be deleted from the generic labeling leaving only the indication for hypertension.
- ⇒ Altace – Awarded exclusivity for the indication of heart failure post myocardial infarction. This indication would be required to be deleted from the generic labeling leaving only an indication for the treatment of hypertension.
- ⇒ Rythmol – Awarded exclusivity for the indication of Paroxysmal Supraventricular Tachycardia (PSVT). This indication would be required to be deleted from generic labeling leaving only the indication for the prolongation of the time of recurrence of Paroxysmal atrial fib/flutter (PAF).
- ⇒ Mevacor – Awarded exclusivity for the indication of primary prevention of coronary heart disease in patients without symptomatic cardiovascular disease who have average to moderately elevated total c and below average HDL-c). The only indication contained in generic firms labeling is the treatment of primary hypercholesterimia.
- ⇒ Leucovorin Inj – Awarded ODE for use in combination with 5FU for the treatment of metastatic colorectal cancer and for rescue after high dose methotrexate therapy in the treatment of osteosarcoma. This indication was carved out of generic drug labeling until the exclusivity expired.
- ⇒ Prozac – Awarded exclusivity for the indication of the Treatment of Bulimia. Generic firms have been requested to delete this indication from their labeling leaving only the indications for depression and obsessive compulsive disorder.

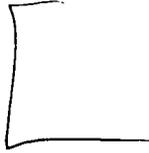
#### IV. LABELING ASSESSMENT:

A patient package insert has been proposed for distribution with this product. However, the applicant has not submitted the labeling. It is difficult to conceptualize the reasons why Betapace AF would require a specialized PPI considering the dosing of both products are essentially identical. When comparing the Betapace and Betapace AF package inserts side-by-side the only differences noted are as follows:

##### CLINICAL PHARMACOLOGY:

Electrophysiology subsection now includes the study results from AFIB/AFL trials.  
Clinical Actions subsection now includes only AFIB/AFL information.

##### INDICATIONS AND USAGE:



##### WARNINGS:

Proarrhythmia subsection now includes the information from controlled trials of patients with AFIB/AFL.

Congestive Heart Failure subsection contains an additional two sentences relating to studies for AFIB/AFL.

Conduction Disturbances subsection contains one sentence relating to bradycardia in the supraventricular arrhythmia population with Betapace AF.

Recent MI subsection now includes a sentence stating 

Sick Sinus Syndrome now includes a paragraph from information gained in the AFIB/AFL studies. 

##### PRECAUTIONS:

Information for Patients subsection has now been added.

Drug Interactions subsection now includes a subsection entitled 

Digoxin subsection now includes a sentence on digitalized patients with AFIB.

Antacids subsection has been added. This subsection is also generic to sotalol. 

##### ADVERSE REACTIONS:

In addition to the information contained in Betapace insert the Betapace AF insert includes information gained in four placebo-controlled studies with patients with AFIB/AFL.

##### OVERDOSAGE:

This section now includes an additional sentence of hypotension following overdose generic to sotalol.

DOSAGE AND ADMINISTRATION:

The Betapace AF insert utilizes common language contained in the insert of Betapace. The differences are due to the clinical studies conducted in conjunction with the new indication and to the treatment of the disease and not related to the drug product. These differences are not unique to product labeling that contains different indications for use.

V. RECOMMENDATIONS:

1. OPDRA recommends that the proprietary name Betapace AF for a new indication of an already approved drug product, not be approved.
2. OPDRA recommends that the proprietary name Betapace be maintained for all indications and that only one package insert is approved that would be inclusive for all indications.
3. OPDRA recommends that NDA 21-151 be collapsed into NDA 19-685 (and be treated as an efficacy supplement). Waxman-Hatch 3 year exclusivity would most likely be granted to Berlex for this new indication. All generic drug products would carve this out of their labeling and would not include a Patient Package Insert.
4. The firm should be asked to choose one formulation (color) to use in marketing Betapace and request withdrawal of the other.
5. OPDRA recommends that the language in the insert (INDICATIONS and USAGE) concerning the inability of substitution be deleted.

If you have any questions concerning this review please contact Carol Holquist at 301-827-3244.

Carol Holquist 11/2/97  
Carol Holquist, RPh.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips 11/2/97  
Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

CC:

Office Files

HFD-110; Mike Johnston, Safety Evaluator, DDRE I, OPDRA

HFD-430; Min Chen, Team Leader, DDRE I, OPDRA

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Peter Honig, Deputy Director, OPDRA

HFD-002; Murray Lumpkin, Acting Director, OPDRA

HFD-600; Doug Sporn. Director OGD

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Division of Cardio-Renal Drug Products

Public Health Service  
Memorandum

Date : September 28, 1999  
From : Director, Division of Cardio-Renal Drug Products, HFD-110  
Subject : Approvability of NDA 21-151, d,l-sotalol, Berlex Labs  
To : Director, Office of Drug Evaluation I, HFD-100

*Lyrically*

Abbreviated Summary

I join Dr. Fenchel (memo of June 4, 1999) and the Cardiac and Renal Drugs Advisory Committee (meeting on April 29, 1999) in recommending that sotalol be approved for delaying the recurrence of chronic atrial fibrillation.

The original submission of the trial results that support approval was a supplement to NDA 19-865, under which Berlex markets d,l-sotalol (Betapace) as a ventricular antiarrhythmic. Since that time, Berlex has decided (and the Agency concurred with that decision) that it would be appropriate for d,l-sotalol to be marketed for the treatment of atrial fibrillation as a completely separate product (Betapace AF), thus NDA 21-151.

As can be seen from the reviews that were previously sent, the clinical development program was adequate, but not optimal. There are 3 parallel, randomized, placebo-controlled trials (only one of which was performed under the sponsor's supervision, the other 2 being supervised by what was then known as Bristol-Myers Squibb; all 3 are now owned by Berlex). We know of one other trial placebo-controlled trial (a trial conducted in support of d,l-sotalol) but to which the sponsor has no right to reference. In all 4 placebo-controlled studies, d,l-sotalol increased the median time to recurrence of atrial fibrillation, compared to placebo. Moreover, there was clearly an increasing effect with increasing dose. Additionally it is important to recall that the current approved package insert for Betapace cites a 1,456 randomized, placebo-controlled secondary prevention trial (post-MI) where mortality was 7.3% in patients receiving d,l-sotalol and 8.9% in patients receiving placebo.

The dose range over which d,l-sotalol has been studied in atrial fibrillation is identical to the dose range currently approved for the treatment of ventricular arrhythmias, namely 80 to 160 mg, twice-a-day.

Dr. Fenchel deals nicely with the issues that have arisen with respect to how to analyze the trials with appropriate attention to drop-outs. I can add nothing to his discussion. There is no doubt in my mind, the data support approval.

Inspections

We are overdue (with respect to User Fee Goals) in our action on this NDA because, as is well documented in the review package, there was question with respect to what to do about what appeared to

be non-uniform results in one trial. A foreign inspection was requested on May 6, 1999 and an inspection summary report was received on August 12, 1999. That report was forwarded to you soon after receipt, but without comment from the Division.

Not unexpectedly, the inspection found problems at both sites that were selected for inspection. The major findings were with respect to documentation, some of which can be explained by existing Swedish law that was in effect when the study was being conducted; some of which can be explained by sloppiness, none of which implies fraudulent or unblinded data.

Five patients at study site #029 had a history of thyroid disease (apparently reasonably treated) and although not protocol violations (the protocol did not stipulate that patients with thyroid disease, active or treated, should be excluded) the inspectors thought they should not have been included in the trial. I disagree.

Two patients at study site #029 received protocol prohibited concomitant medications (one atenolol and another digoxin). I would not have had those medications prohibited, if I had written the protocol. So, I see no problem with this.

Also at study site #029, 4 patients had evidence of decompensated heart failure, all in the placebo group. These patients were said to be compensated during the trial, but the inspection could find no documentation of compensation, only verbal reports. I see no problem with having patients with congestive heart failure in the trial.

At study site #006 one patient received concomitant amiodipine. That, should not have been a prohibition in the protocol.

As a consequence, the Division of Scientific Investigation recommended that a re-analysis of the trial be conducted with 12 patients excluded from the analysis. We have not done that, nor do I think it necessary. I have yet to see a foreign inspection that does not find some problem with documentation, yet I think the European investigators are as good and produce results as honest as their U.S. counterparts. The specific "protocol violations" and/or medical reasons for raising complaints are not what I think are reasonable. The problem, if there was one, was with how the protocol was written. The observed problems are not problems, in my judgement a problem. Excluding these patients would be an arbitrary decision.

What is a Name

Berlex would like to market d,l-sotalol for the treatment of atrial fibrillation as Betapace AF (with a new package insert and a patient package insert), to distinguish it from Betapace (leaving the original package insert as it is). I think that is a fine idea.

Although I have seen nothing in writing, I understand that others within the Agency think the name Betapace AF is not acceptable. For what it is worth, if it is within my power to do so, I over rule that notion. Betapace AF is a totally acceptable name, in my judgement.

cc: Div File  
McDonnell

See back →

DF

What To Do Now ?

It has been some time since we forwarded the review package to you, the delay being determined primarily awaiting the inspection results. As best as I recall, everything is in order. If there is anything we need to do, in order to help your review, please let us know.

OCT - 4

MEMORANDUM

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

DATE:

MAY 3 1999

FROM:

Joan C. Standaert, Executive Secretary  
Cardiovascular and Renal Drugs Advisory Committee

SUBJECT: 88th Meeting of the Cardiovascular and Renal Drugs Advisory Committee, April 29-30, 1999:  
INFORMATION ALERT MEMORANDUM

TO: Director, Center for Drug Evaluation and Research, HFD-1

The Committee met in open session on April 29, 1999 to discuss NDA 19-865, Betapace (d,l-sotalol hydrochloride), Berlex Laboratories, to be indicated for maintenance of sinus rhythm in patients who have been converted from atrial fibrillation. Betapace is a beta-blocker with Class III antiarrhythmic activity. It is approved for the treatment of life-threatening ventricular arrhythmia and has been marketed in the U.S. for that indication since 1993.

The sponsor presented the results of two primary clinical trials: 05, a multicenter, double-blind, placebo-controlled, fixed dose, parallel-group, randomized, dose-response study of 253 subjects and, 004, a multicenter, randomized, double-blind, placebo-controlled, parallel-group evaluation of oral d,l-sotalol and d-sotalol in 349 subjects. Two supporting studies, 014 and 9A, were also described.

In response to questions asked by the FDA, the Committee concluded that the sponsor had identified a dosing strategy, 80 mg b.i.d., titrated to 160 mg b.i.d., that convincingly alleviated symptoms or reduced incidence of stroke. Side effects like torsade de pointes and QT prolongation were dose dependent. d,l-sotalol appeared to be similar in efficacy to other approved agents for this indication. One side effect, bradycardia, was thought to be more common with d,l-sotalol. The Committee recommended 6-yes, 3-no, that d,l-sotalol be approved to delay the frequency of relapse of atrial fibrillation in patients with significant symptoms.

The committee recommended that initiation of therapy be started in the hospital, with dose based on calculated creatinine clearance, and that treatment be contraindicated in patients on other beta blockers or with bradycardia or overt heart failure. Labeling should indicate that d,l-sotalol is intended as a treatment for cardioverted patients in normal sinus rhythm, not as a treatment for atrial fibrillation.

On April 30, the Committee discussed drug trials utilizing patients with implanted cardioverter-defibrillators. The participants discussed the difficulties of interpreting such trials. Their usefulness in clinical trials for antiarrhythmic agents will require further refinement and standardization.

Distribution:

HFD-2 Deputy Director for Review Management  
HFD-3 Deputy Director for Pharmaceutical Science  
HFD-4 Associate Director for Medical Policy  
HFD-5 Associate Director for Policy  
HFD-6 Executive Operations Staff  
HFD-7 Regulatory Affairs Staff  
HFD-21 Advisors and Consultants Staff  
HFD-21 J. Treacy, Advisors and Consultants Staff  
HFD-101 Director, Office of Drug Evaluation I  
HFD-101 Special Assistant, ODE I  
HFD-110 Director, Division of Cardio-Renal Drug Products  
HFD-110 Executive Secretary of Cardio-Renal Drug Advisory Committee  
HFD-120 Director, Division of Neuropharmacological Drug Products  
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HFD-850 Director, Office of Clinical Pharmacology & Biopharmaceutics  
HFD-900 Director, Office of Testing & Research  
HF-35 Director, Orphan Products Development  
HFE-40 Policy Analysis Staff  
GCF-1 General Counsel  
HFA-224 Records Retrieval Unit

See attached volumes

<b>NDA:</b>	21-151
<b>Drug:</b>	Betapace (sotalol) Tablets
<b>Applicant:</b>	Berlex Laboratories
<b>Chem/Ther/other Types:</b>	6S
<b>CSO/PM:</b>	Zelda McDonald
<b>Phone:</b>	594-5333
<b>HFD:</b>	110
<b>USER FEE GOAL DATE:</b>	June 22, 1999
<b>CHECKLIST COMPLETE:</b>	2-18-00

Arrange package in the following order (include a completed copy of this CHECKLIST):

1. ACTION LETTER with supervisory signatures	AP			
Are there any Phase 4 commitments?		No		
2. Have all disciplines completed their reviews?	Yes			
3. LABELING (package insert and carton and container labels). Note: If final or revised draft, include copy of previous version with ODEs comments and state where in action package the Division's review is located. If RX-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.		Revised Draft		
4. PATENT INFORMATION	Yes			
5. EXCLUSIVITY CHECKLIST	Yes			
6. PEDIATRIC PAGE (all NDAs)	Yes			
7. DEBARMENT CERTIFICATION (copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	Yes			
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES. Note: If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why.	Yes			
9. REVIEWS & MEMORANDA				
a. DEPUTY DIVISION DIRECTOR'S MEMO	Yes			
b. GROUP LEADER'S MEMO	Yes			
c. MEDICAL REVIEW	Yes			
d. SAFETY UPDATE REVIEW	Yes			
e. STATISTICAL REVIEW	Yes			
f. BIOPHARMACEUTICS REVIEW	Yes			
g. PHARMACOLOGY REVIEW (Include pertinent IND reviews)	NA			
1) Statistical Review of Carcinogenicity Study(ies)	NA			
2) CAC Report/Minutes	NA			
h. CHEMISTRY REVIEW	Yes			
1) Labeling and Nomenclature Committee Review Memo	Yes			
2) Date EER completed	NA			
3) EER Results (attach signed form or CIRT's printout)	NA			
4) FUR needed	NA			
5) FUR requested	NA			
6) Have the methods been validated?	NA			
7) Environmental Assessment Review	Excl.			
8) FONSI	NA			

i. MICROBIOLOGY REVIEW	NA		
1) What is the status of the monograph?			
10. CORRESPONDENCE, TELECONS, and FAXes	Yes		
11. MINUTES OF MEETINGS	Yes		
a. Date of End-of-Phase 2 Meeting:			
b. Date of pre-IND Meeting:	2/12/98		
12. ADVISORY COMMITTEE MEETING			
a. Meeting Conducted	Yes		
b. Minutes		No	
c. Info Alert	Yes		
d. Transcript		No	
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS		No	
14. If AP letter, has ADVERTISING MATERIAL been reviewed?		No	
a. If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes, documentati on attached		
15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)	Yes		
16. INTEGRATED SUMMARY OF SAFETY (from NDA)	Yes		

zm

dup

MAR 16 1998

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
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1451 Rockville Pike  
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**Transmitted to FAX Number:** 973-276-2016  
**Attention:** Ms. Maria Garrigan - Please let me know you received this. Thanks!  
**Company Name:** Berlex  
**Phone:** 973-276-2193  
**Subject:** Minutes of 2/12/98 Meeting  
**Date:** 3/16/98  
**Pages including this sheet:** 4

**From:** Zelda McDonald  
**Phone:** 301-594-5333  
**Fax:** 301-594-5494

cc:  
Orig. IND  
HFD-110  
HFD-110/McDonald

Meeting Minutes

MAR 16 1998

Meeting Date: February 12, 1998  
Meeting Requested: January 15, 1998 (telephone)

IND# 2,544 (dl-sotalol H Cl)  
Sponsor: Berlex  
Type of Meeting: Pre-Supplemental NDA

Meeting Chair: Abraham Karkowsky, M.D.  
Meeting Recorder: Zelda McDonald  
External Participant Lead: Maria Garrigan

FDA Participants:

Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Khin Maung U, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Statistician, HFD-710
Zelda McDonald	RHPM, HFD-111

Berlex Participants:

Wanju Dai, M.D., Dr. P. H.	Dir. Epidemiology & Outcomes Research, Dept. of Epidemiology and Medical Affairs
Kishor A. Dandekar, Ph.D.	Associate Director, Clinical Pharmacology
Maria Garrigan	Regulatory Administrator, Drug Regulatory Affairs
Judy Jin, Ph.D.	Head Statistician, Clinical Cardiovascular Research
Prannath Marrott, M.D.	Director, Clinical Cardiovascular Research
Joseph Posluszny, Ph.D.	Director, Project Manager, Cardiovascular
John Williams, M.D.	Senior Associate Medical Director, Cardiovascular Research

Background:

The IND 2,544 for dl-sotalol HCl was submitted on March 29, 1965 by Bristol-Myers Squibb. The submissions of November 16, 1992 (Serial No. 092) and May 26, 1993 (Serial No. 098) transferred all rights and responsibilities for IND 2,544 to Berlex Laboratories, Inc. The NDA 19-865 was approved on October 30, 1992 for the use of dl-sotalol in treating life threatening ventricular arrhythmias. On November 12, 1992 the ownership of NDA 19-865 was transferred from Bristol-Myers Squibb to Berlex Laboratories. Berlex requested this meeting to discuss the content and format of a supplement to NDA 19-865 that Berlex is planning to submit in mid-1998. This supplement is planned to support the following new indication: maintenance of sinus rhythm in patients with symptomatic atrial fibrillation (AFIB)/atrial flutter (AFL).

**Discussion Points/Recommendations/Agreements Reached:**

- A. Does the Division concur that information to be included in Item 4 (Chemistry, Manufacturing and Controls) will be acceptable for the filability of the efficacy supplement to NDA 19-865? (See page 9 of the Pre-Meeting Package).
- The Division concurred but noted that Berlex should call Dr. Short directly with any questions.

B. Does the Division concur that information regarding Item 5 (Nonclinical Pharmacology), and Item 7 (Microbiology) is not relevant to this efficacy supplement to NDA 19-865? (See pages 10 and 15 respectively of the Pre-Meeting Package.)

- The Division concurred but asked Berlex to include any studies they may have conducted or reprints they may have on animal studies in supraventricular arrhythmias. It would be nice to include such information, however, it is not required.

C. Does the Division concur that the proposed overview summary of the human pharmacokinetics and bioavailability of dl-sotalol (Item 6) will be acceptable for filability of the efficacy supplement for NDA 19-865? (See pages 11 to 14 of the Pre-Meeting Package.)

- The Division concurred.

D. Clinical and Statistical (See pages 16 to 27 of the Pre-Meeting Package).

1. Does the Division concur with the proposed format of Item 8 and the studies to be included in this Item?

- The Division concurred noting that previously submitted studies do not need to be submitted again.

2. Does the Division concur that the proposed Integrated Summary of Efficacy will be adequate to support the filability of the supplement to NDA 19-865 with specific regard to:

a) The greater emphasis Berlex will place on the analysis of the two major studies (106-05) and CV102-004) with the remaining studies provided as supportive.

- The Division will look at all studies that are equivalent in size despite which studies Berlex selects as major. Berlex confirmed that the Division will have access to the database although the electronic database will consist only of the two major studies and the one study that converted — The other studies have already been reviewed. Berlex agreed to submit a detailed report on study 014 since the Division will be reviewing that study for safety.

b) That the efficacy claim will be based on the Intent-To-Treat population (all randomized patients) in the two pivotal studies.

- The Division requested an analysis of the Intent-To-Treat population from the time of randomization as well. Berlex agreed to provide both analyses.

c) Transfer of electronic data from the two major studies only to the Division?

- The Division requested that all available data from all controlled trials be submitted in electronic format. Berlex believed that the studies done by Bristol-Myers Squibb would not be available in electronic format, but

the integrated summaries of safety and efficacy would be provided as a CANDA in WORD format.

3. Does the Division concur that the proposed Integrated Summary of Safety will be adequate to support the filability of the Supplement to NDA 19-865 in that Berlex will place greater emphasis on the pooled computerized safety database composed of the following four studies: 106-05, CV102-004, CV101-014, 02A9a-001; with the remaining studies presented individually?

- The Division will do their own analyses and will pool all data. Dr. Karkowsky will check with Dr. Lipicky to see if a point estimate for mortality will be needed. (Dr. Lipicky does not believe that the data base will be powered to come to any conclusion.)

- E. Does the Division concur that for Item 11, the proposed cross-references to the patient listings contained in the appendices to each clinical study will be adequate to support the filability of the supplement to NDA 19-865? (See page 30 of the Pre-Meeting Package).

- The Division concurred.

- F. Berlex asked if the Division wanted additional categories analyzed other than what were listed on page 26 of the Pre-Meeting Package.

- The Division requested that "renal disease" be included.

- G. Berlex asked what studies would be needed in order to obtain labeling claim for use of dl-sotalol in children.

- If Berlex wanted to claim efficacy, they would need a placebo controlled trial that showed efficacy. If Berlex only wanted to do a PK/PD study, it would be described in the Clinical Pharmacology section of the package insert. All dosing would be described in the Dosage and Administration section.

Signature minutes preparer:

*Zelda McDonald 3/16/98*

Concurrence, Chair:

*John Karkowsky 3/16/98*

Orig. IND  
HFD-110  
HFD-111/McDonald  
HFD-111/Benton

Drafted 2/18/98      Finaled 3/16/98

RD

Karkowsky    1/13/98  
Hung         2/19/98  
U             2/19/98  
Short        3/13/98  
El Tahtawy   3/16/98