CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-865/S-010

Administrative Documents

EXCLUSIVITY SUMMARY FOR NDA # _19-865_____ SUPPL #__010____

Trade Name _Betapace_____ Generic Name _Sotalol_____

Applicant Name _Berlex_____ HFD # ___110_____

Approval Date If Known __October 1, 2001_____

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 /_X__/

b) Is it an effectiveness supplement?

YES /_X__/ NO /___/

If yes, what type? (SE1, SE2, etc.) ___SE8_____

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 /_X__/ 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:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

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

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

_____Yes_____

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 /_X__/

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 /_X__/

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 /_X__/ NO/___/

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

NDA# _19-865 This 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 /_X__/ 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 /_X__/ 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:

_____

(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 /_X__/

(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 /_X_/

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 /_X__/

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 # 98173 – PK Study

Study # 98217 – PK/PD Study

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 /_X__/

Investigation #2

YES /__/ NO /_X__/

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 /_X__/

Investigation #2 YES /___/ NO /_X__/

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"):

Same as #2(c)_____ _____

_____ _____

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 #) YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND #) YES /_X__/ NO /___/ Explain: _____

(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 /_X__/

If yes, explain: _____

_____

/S/

Signature Date
Title:

/S/

Signature of Office/ Division Director Date 11/27/01

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	019865	**Trade Name:**	BETAPACE TABLETS
Supplement Number:	010	**Generic Name:**	SOTALOL HYDROCHLORIDE
Supplement Type:	SE8	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	VENTRICULAR ARRHYTHMIAS
Action Date:	10/19/99		

Indication # 1 Ventricular arrhythmias/supraventricular arrhythmias
Label Adequacy: Adequate for ALL pediatric age groups
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any): Response to pediatric written request.

Lower Range	Upper Range	Status	Date
0 years	Adult	Completed	

This page was last edited on 1/29/01

/S/

Signature

1/29/01

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — **Public Health Service**
Division or Cardio-Renal Drug Products — **Memorandum**

Date : December 29, 2000
From : Director, Division of Cardio-Renal Drug Products; HFD-110
Subject : Approvability of NDA 19-865 SE 8-010, Pediatric, *d,l*-Sotalol , Berlex Labs
To : NDA File

This supplement was in response to our letter to Berlex requesting pediatric studies. The sponsor did exactly as we requested, and exclusivity has already been awarded.

The request that we made was not intended to result in clinical trials that would establish the safety and efficacy of *dl*-sotalol in any pediatric population for any cardiac arrhythmia. Sotalol has two properties (effects on heart rate from beta blockade and effects on the QT interval from effects on electrically excitable channels) that allow the pharmacodynamic effects as a function of plasma concentration to be evaluated in a pediatric population. These effects in adults have been reasonably characterized as a function of dose.

The pharmacokinetic properties, as a function of dose, are also able to be easily evaluated. Thus both the pharmacokinetic and pharmacodynamic behavior of *dl*-sotalol in children can be examined and used to write appropriate instructions for use. Such information is far more informative than that which existed prior to the work reported in this supplement.

Dr. Karkowsky is correct in his evaluation of this submission; the safety and effectiveness of *dl*-sotalol have not been established. Useful dosing information, however, has been gained and should be incorporated into labeling. Its inclusion in labeling will provide for more appropriate use of an already used therapy. Omitting this information will not discourage off-label use, omission would simply contribute to use that is more inappropriate. The studies submitted have added useful information.

The submitted draft labeling has been marked up, and is satisfactory, except for the Dosage and Administration section. This should be modified as follows.

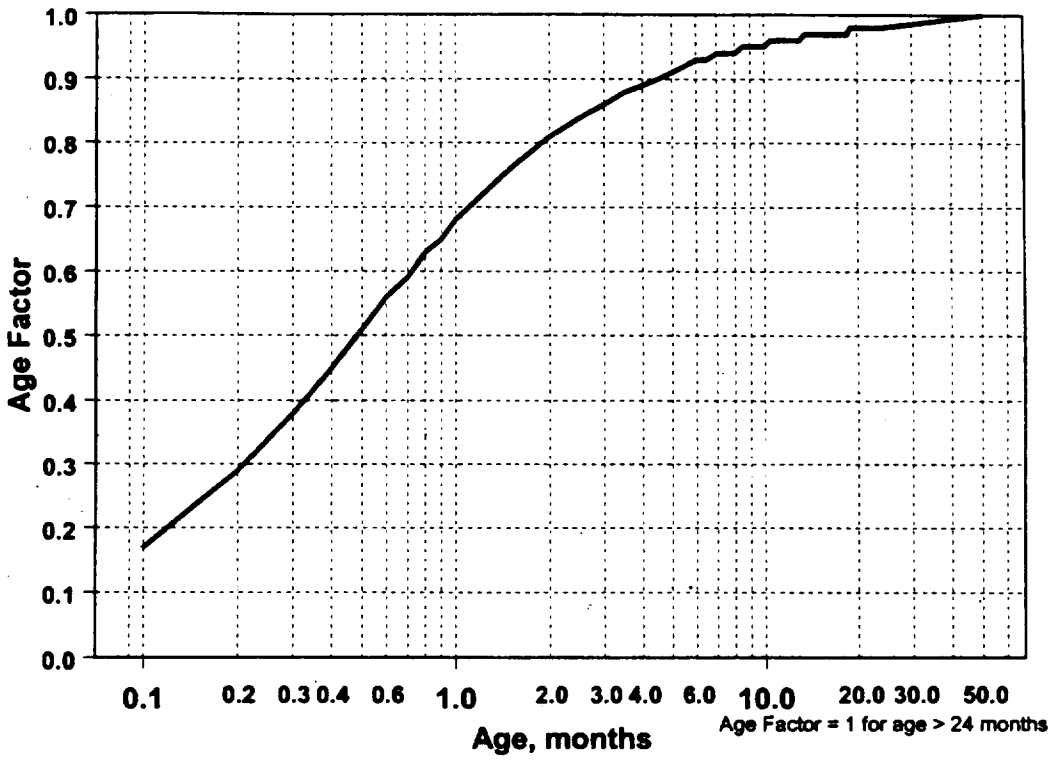
For the Dosage and Administration section
The 1st paragraph can be exactly as submitted by the sponsor.

The second and 3rd paragraphs of the sponsor's submission should be replaced by what follows.

DRAFT

a maximum of 60 mg/m^2 (approximately equivalent to the 360 mg total daily dose for adults) can then occur. Titration should be guided by clinical response, heart rate and QTC, with increased dosing being preferably carried out in-hospital. At least 36 hours should be allowed between dose increments to attain steady state plasma concentrations of sotalol.

For children aged about 2 years or younger the above pediatric dosage should be reduced by a factor that depends heavily upon age, as shown in the following graph, age plotted on a logrhythmic scale in months.



For a child aged 20 months the dosing suggested for children with normal renal function aged 2 years or greater, should be multiplied by about 0.97; the initial starting dose would be (30 X 0.97)=29.1 mg/m^2, administered three times daily. For a child aged 1 month, the starting dose should be multiplied by 0.68; the initial starting dose would be (30 X 0.68)= 20 mg/m^2, administered three times daily. For a child aged about 1 week, the initial starting dose should be multiplied by 0.3; the starting dose would be (30 x 0.3) 9 mg/m^2. Similar calculations should be made for increased doses as titration proceeds. Since the half-life of sotalol decreases with decreasing age (below about 2 years), time to steady state will also increase. Thus, in neonates the time to steady state may be as long as a week or longer.

The influence of decreased renal function in any pediatric population has not been studied but sotalol elimination is predominantly via the kidney in the unchanged form. Use of sotalol in any age group with decreased renal function should be at lower doses and at decreased intervals

between doses. Monitoring of heart rate and QT_C is more important, and it will take much longer to reach steady state with any dose and/or frequency of administration.

In all children, individualization of dosage is required. As in adults BETAPACE (sotalol hydrochloride should be used with particular caution in children if the QT_C is greater than 500 msec on therapy and serious consideration should be given to reducing the dose or discontinuing therapy when QT_C exceeds 550 msec.

APPEARS THIS WAY
ON ORIGINAL

/s/

Raymond Lipicky
3/14/01 10:03:55 AM
MEDICAL OFFICER