

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-437/S-002

Administrative/Correspondence

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: 21-437	Efficacy Supplement Type: SE-1	Supplement Number: 002
Drug: Inspra 25, 50 & 100 mg Tablets		Applicant: G.D. Searle LLC
RPM: Mr. Daryl Allis		HFD-110 Phone # 301-594-5309
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): 21-437 Inspra
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		N/A
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Date		October 7, 2003
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid; ID # 4525
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Yes
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager) (indicate date of each review)	October 7, 2003
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	Approved for HTN on 9/27/02
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release (X) Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Enclosed in the Approval letter
• Most recent applicant-proposed labeling	October 7, 2003 (email attachment)
• Original applicant-proposed labeling	April 3, 2003
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	Office Briefing: Dr. Temple 9/2 Internal mtgs.: 8/21; 9/5; 9/25 Sponsor meetings: 9/26; 10/1
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Inspira for HTN; Aldactone
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	April 20, 1999
• Pre-NDA meeting (indicate date)	January 9, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Filing Meeting May 22, 2003

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	October 6, 2003
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	October 3, 2003
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Incorporated into the clinical review (deaths are in the discussion of the primary endpoint and safety data are in the integrated review of safety).
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	Yes
❖ Statistical review(s) (indicate date for each review)	August 25, 2003
❖ Biopharmaceutical review(s) (indicate date for each review)	September 4, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	September 2, 2003
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	September 2, 2003
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A () Acceptable () Withhold recommendation
❖ Methods validation	() Completed N/A () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	September 2, 2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daryl L. Allis .
10/7/03 04:52:30 PM

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



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: 847-982-8090

Attention: **Dr. Lynne Weissberger**

Company Name: G.D. Searle LLC

Phone: 847-982-7469

Subject: NDA 21-437/S-002 Approval Letter
Date: October 7, 2003

Pages including this sheet: 35

From: **Daryl Allis**
Phone: 301-594-5309
Fax: 301-594-5494
E-mail: allisd@cder.fda.gov

Please let me know you received this.

Thank you.

RHPM Overview of NDA 21-437/S-002

Inspra (eplerenone) Tablets

October 7, 2003

Sponsor: G.D. Searle LLC
Type: SE1 / P
Receipt Date: April 7, 2003
User Fee Goal Date: October 7, 2003
AP Letter Issued: October 7, 2003
Final Draft Labeling: Received via e-mail attachment, October 07, 2003

Background

Inspra (eplerenone) is a selective aldosterone receptor antagonist (SARA). It is a steroid nucleus-based antimineralocorticoid that effectively blocks aldosterone at receptor sites in tissues throughout the body, thereby antagonizing the pathological effects of inappropriate aldosterone levels while limiting side effects associated with nonspecific steroid receptor binding. The original NDA for Inspra was approved on September 27, 2002 for the treatment of hypertension. This supplemental application was submitted electronically in the Common Technical Document format for the indication to reduce the risk of death (principally by reduction in cardiovascular death) and cardiovascular hospitalization in stable patients with left ventricular dysfunction and clinical evidence of heart failure after an acute myocardial infarction. Cardiovascular hospitalization is defined as hospitalization for progression of heart failure, myocardial infarction, stroke, or ventricular arrhythmias.

Previous correspondence and meetings regarding the development of Inspra for the indication for heart failure include:

1. EOP 2 meeting for heart failure on April 20, 1999
2. Pre-sNDA meeting on January 9, 2003

Division Director's Memorandum

In his Divisional memorandum dated October 6, 2003, Dr. Throckmorton stated, the EPHEBUS trial of eplerenone, reinforced by the data on aldactone in the RALES trial, provides a robust demonstration of eplerenone's effects to reduce mortality in patients with CHF after myocardial infarction. A less convincing effect of eplerenone on hospitalization was suggested. No demonstrated effects of eplerenone on other measures of benefit (e.g., symptoms) were shown. The trial identified no novel safety concerns for the patients with CHF, and the use of the product, like its use in hypertension, will likely be limited to some extent by the development of hyperkalemia. Approval of the supplement will make a novel class of agents in the treatment of CHF available to patients, and this trial represents an important advance in therapy. No outstanding issues remain, including labeling, for this supplemental NDA.

Medical Review

In his review dated October 3, 2003, Dr. Marciniak concluded, Inspra (eplerenone) produced a 15% reduction ($p=0.008$) in mortality in a large trial in patients with congestive heart failure (HF) following acute myocardial infarction (MI). The major potentially serious adverse effect, hyperkalemia, was managed by monitoring potassium levels and adjusting dosage so that rates of serious hyperkalemia were low. From a clinical perspective, he recommends approval of eplerenone to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction $\leq 40\%$) and clinical evidence of HF post-MI.

There are no recommended mandatory phase 4 studies. There are unanswered questions regarding eplerenone use that, if elucidated, would help to improve its usability. Some questions are relevant to the HF post-MI indication of this sNDA and others are more relevant to the hypertension indication. Questions relevant to the HF post-MI indication are regarding dosage, dosing interval, duration of treatment, and effectiveness in the very elderly. Questions relevant to the hypertension indication are

whether eplerenone has any effects upon breast cancer incidence, thyroid dysfunction, or adrenal adenoma development. Equally important as these questions is the issue of whether the benefit of eplerenone in HF post-MI extends to other HF populations, i.e., ones not immediately post-MI.

Financial Disclosure is addressed on page 50 of the medical review.

Dr. Marciniak's recommendations regarding the proposed labeling are on pages 156 to 184 of the medical review.

The Safety Update Review is incorporated into the medical review. The deaths are included in the discussion of the primary endpoint and the safety data are incorporated into the Integrated Review of Safety.

Statistical Review

In his review dated August 25, 2003, Dr. Hung concluded, based on the EPHEBUS results, eplerenone yielded a statistically significant reduction (15%, 95% CI: 4%-25%, $p = 0.008$) in mortality, mostly CV mortality (17%, 95% CI: 6% - 28%). There was no evidence that eplerenone reduced the incidence of non-CV death. For the other co-primary efficacy endpoint – CV mortality/hospitalization, the final definition of CV hospitalization was established in the late stage of the trial (a few months before the trial ended). It is not clear whether the modification of CV hospitalization was ever influenced by examination of the trial data. Dr. Marciniak has concerns with the definition of CV hospitalization. By taking this endpoint as it is, there was a statistically significant reduction in favor of eplerenone ($p = 0.002$). All cause mortality/hospitalization appeared to reach borderline statistical significance. Numerically, eplerenone seemed to have a favorable effect on mortality in the US.

Pharmacology Review

In her review dated September 3, 2003, Dr. Hausner stated there are no preclinical issues to preclude approvability. There were no new toxicology studies submitted with this supplemental application. The pharmacology/toxicology review for NDA 21-437 (approved September 27, 2002) was referenced. The proposed labeling regarding findings _____ should be removed.

Biopharmaceutical Review

In her review dated September 4, 2003, Dr. Mishina stated this supplemental NDA included the data for the following clinical studies to evaluate whether the pharmacokinetics of eplerenone in patients with symptomatic heart failure is comparable to that in healthy volunteers and if any dose adjustment is warranted for the patient with congestive heart failure:

- "Effect of Chronic Congestive Heart Failure on the Pharmacokinetics of Eplerenone"
- "Dose-Ranging Study of Eplerenone vs. Placebo in Patients with Symptomatic Heart Failure" (EPHEBUS Study, IE3-99-02-035), population pharmacokinetics sub-study

The Office of Clinical Pharmacology and Biopharmaceutics recommends adopting the proposed language for the labeling.

Chemistry Review

In his review dated September 2, 2003, Dr. Chidambaram stated this supplemental application has cross-referenced the entire chemistry, manufacturing and controls (CMC) information that was submitted in the original NDA (approved September 27, 2003) and there are no changes to the manufacturing process or the manufacturing site(s) that were submitted in the original NDA. There are no proposed chemistry changes to the Description, Dosage and Administration, and How Supplied sections of the labeling. The applicant's claim for categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (a) is acceptable. This supplemental application is recommended for approval from the standpoint of chemistry, manufacturing and controls.

DSI

There were no scheduled clinical site reviews for this supplemental application.

C

J

Labeling:

The sponsor submitted final printed labeling for Inspra on May 21, 2003 in response to our September 27, 2002 approval letter for the original NDA 21-437 Inspra (eplerenone) 25, 50 and 100-mg Tablets for the treatment for hypertension. The Division issued an acknowledge and retain letter on June 25, 2003 stating the labeling is acceptable.

The sponsor submitted electronic draft labeling that included their proposed labeling for heart failure. The sponsor's most recent proposed labeling, dated October 7, 2003, is included in the action package. In addition, the sponsor informed the Division that they have decided not to manufacture Inspra 50-mg Hospital Unit Dose blister packages and Inspra 100-mg tablets. They, therefore, have deleted the 50-mg Hospital Unit Dose and the Inspra 100-mg Tablets in the How Supplied section of the proposed labeling. The sponsor will report these changes in the annual report for NDA 21-437 Inspra (eplerenone) Tablets. Dr. Srinivasachar, Team Leader Chemistry, concludes these changes are acceptable. This supplemental NDA will be approved on draft labeling.

Advisory Committee Meeting

No meeting held.

Project Manager's Summary

To my knowledge, there are no issues that might prevent action on this supplemental NDA.

Daryl Allis, RHPM

40 pages redacted from this section of
the approval package consisted of draft labeling

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS G.D. Searle LLC 4901 Searle Parkway Skokie, IL 60077	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-437
2. TELEPHONE NUMBER (include Area Code) (847) 982-7469	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Inspra (eplerenone tablets)	6. USER FEE I.D. NUMBER 4525

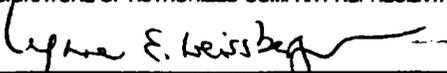
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 738(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 738(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parkdown Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Associate Director, Global Regulatory Affairs	DATE 04-April-2003
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NDA 21-437
CERTIFICATION UNDER 21 CFR 314.53(d)(2)(ii)

G.D. Searle LLC hereby certifies that the following patent(s) that were previously submitted under this NDA cover the changes that are the subject of the present Supplemental NDA:

Patent No.	Expiration Date
4559332	April 9, 2004
6410054	December 8, 2019
6495165	December 8, 2019

G.D. Searle LLC

By: 

Carl W. Battle

Title: Attorney-in-fact

Date: March 4, 2003

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 years

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 / 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# 21-437 Inspra for HTN _____

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 / / N/A X

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:

IE3-99-02-035

IE3-97-02-011

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"):

IE3-99-02-035 _____

IE3-97-02-011 _____

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 # 51,780 YES / X / NO / ___ / Explain: _____

Investigation #2

IND # 51,780 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 NA

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: _____

Thomas Marciniak, M.D.
Medical Officer

9/16/03
Date

Douglas C. Throckmorton, M.D.
Division Director

10/07/03
Date

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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doug Throckmorton
10/7/03 04:05:30 PM

NDA 21-437

CLAIM FOR EXCLUSIVITY UNDER 21 CFR 314.108(b)(4) or (b)(5)

GD Searle LLC is hereby claiming three (3) years of exclusivity under (check one):

- 21 CFR 314.108(b)(4) (NDA) or
 21 CFR 314.108(b)(5) (Supplemental NDA)

New Clinical Investigations

To the best of Pharmacia's knowledge, each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in Sec. 314.108(a).

Essential to Approval (check one)

Pharmacia hereby certifies that it has thoroughly searched the scientific literature for published studies or publicly available reports of clinical investigations that are relevant to the conditions for which Pharmacia is seeking approval.

1) Attached hereto is list of all published studies or publicly available reports of clinical investigations known to Pharmacia through the above literature search. To the best of Pharmacia's knowledge, the list is complete and accurate and, in Pharmacia's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Pharmacia is seeking approval without reference to the new clinical investigation(s) in the application. Also attached hereto is an explanation as to why the studies or reports are insufficient.

2) The literature search did not provide any published studies or publicly available reports of clinical investigations that are relevant to the conditions for which Pharmacia is seeking approval.

Conducted or Sponsored By (check one)

3) Pharmacia was the sponsor named in the Form FDA-1571 for an investigational new drug application (IND) under which the new clinical investigation(s) that is essential to the approval of its application was conducted. IND # 51,780

4) Pharmacia certifies that it or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its application. A certified statement from a certified public accountant that Pharmacia provided 50 percent or more of the cost of conducting the study is attached.

5) An explanation of why the FDA should consider Pharmacia to have conducted or sponsored the study if Pharmacia's financial contribution to the study is less than 50 percent or Pharmacia did not sponsor the investigational new drug is attached.

GD Searle LLC

By: Lyman E. Lewis, Ph.D.

Title: Associate Director

Date: 03/04/03

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

√BLA #: 21-437 Supplement Type (e.g. SE5): SE1 Supplement Number: 002

Stamp Date: April 7, 2003 Action Date: October 7, 2003

HFD- 110 Trade and generic names/dosage form: Inspira (eplerenone) 25, 50 and 100-mg Tablets

Applicant: G.D. Searle LLC Therapeutic Class: Priority

Indication(s) previously approved: Hypertension (September 27, 2002)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

udies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. <1 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

Adult studies ready for approval

Other: _____ The Division stated that we can not comment on the requirement for pediatric studies at this time: appropriate.

Date studies are due (mm/dd/yy): 08/17/06

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Daryl Allis
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daryl L. Allis
10/7/03 03:45:17 PM

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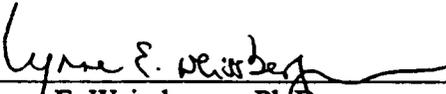
commercial

information

May 2003

DEBARMENT STATEMENT

Pursuant to section 306 (k) of the Federal Food, Drug and Cosmetic Act, the applicant did not and will not employ or otherwise use in any capacity the services of any person debarred under subsection (a) or (b) in connection with this application.



Lynne E. Weissberger, Ph.D.
Associate Director, Global Regulatory Affairs

05/05/03
Date

NDA 21-437/S-002

Inspra (eplerenone) Tablets

There were no clinical site reviews conducted.



Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5365, FAX (301) 594-5494

Divisional Memorandum

DATE: 10.03.03
FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110
SUBJECT: NDA 21-437/ S-002
NAME OF DRUG: Inspira (Eplerenone)
SPONSOR: G.D. Searle, L.L.C.

DOCUMENTS USED FOR MEMO:

1. Project Manager Overview by Daryl Allis, R.H.P.M., dated 10.03.
2. Medical Review by Thomas Marciniak, M.D., dated 10.03.03.
3. Chemistry Review by Nallaperumal Chidambaram, Ph.D., dated 8.26.03.
4. Clinical Pharmacology and Biopharmaceutics Review by B. Nhi Nguyen, Pharm.D., dated 4.10.03.
5. Statistical Review of Clinical Data by H.M. James Hung, Ph.D., dated 8.25.03.
6. Clinical Pharmacology Review by Elena Mishina, Ph.D., dated 9.03.03.
7. Pharmacology/Toxicology Review by Elizabeth Hausner, Ph.D., dated 9.2.03.
8. Debarment Certification dated 5.05.03 from sponsor.
9. No DSI audits were requested or performed.
10. Labeling with proposed and/or accepted changes through 9.30.03.

CONCLUSIONS

This memorandum constitutes the Divisional memorandum decision of an approval action for the NDA efficacy supplement named above for eplerenone in the treatment of congestive heart failure (CHF), based on the results of the EPHEUS trial and supported by the RALES trial data using a pharmacologically-similar drug (aldactone). As summarized below, no outstanding issues remain, including labeling.

BACKGROUND AND OVERVIEW

This submission is focused on the results of the EPHEUS trial in patients with signs or symptoms of congestive heart failure (CHF) post-MI. There are a few points to emphasize from the results:

- 1) While there were ultimately two co-primary endpoints, including one that focused on a combination of mortality and hospitalizations, the primary effect demonstrated in the trial was on mortality. As summarized by Dr. Marciniak, in EPHEUS there was a reduction in cardiovascular mortality of around 13% was seen in the group treated with eplerenone, with about 2/3 of this effect seen in the first 30 days of treatment (see his figure, page 14). Beyond 30 days, the two curves are parallel, with no evidence of either augmented effect over time or a loss of treatment benefit (also discussed by Dr. Hung in his review). In contrast, in the RALES trial, using aldactone in a slightly different CHF population, the reduction in mortality seen with active treatment was 30% (table 71 of the medical review).

- 2) The effects of eplerenone on hospitalization were less clear. An effect of eplerenone to reduce hospitalizations, especially hospitalizations ascribed to cardiovascular causes, was suggested by the data. Absent other data supporting this effect, however, I deem it insufficient to include as an indication for the use of eplerenone.
- 3) The sponsor measured a large number of biomarkers (e.g., BNP levels, interleukin levels, ventricular dimensions on ECHO) and intermediate endpoints (e.g., symptom scores) in an attempt to tie the effects on mortality to less 'final' endpoints and to the proposed effects of aldosterone receptor blockade. The effects on symptoms were neutral, and the observed trends on NYHA Class progression were unconvincing (see below). No mechanism for the effect of eplerenone on mortality was identified; in specific, no evidence for some of the putative mechanisms for the effects of aldosterone receptor blockade (e.g., prevention of collagen formation) were found. Dr. Marciniak has proposed that a large part of the effect was related to the increases in serum K seen in patients taking eplerenone and the data are relatively compelling that this was contributory.
- 4) The effects of eplerenone extended to most of the relevant subpopulations, with the exception of the elderly, where less treatment benefit was seen, and Blacks, where few patients were enrolled. In the latter group, however, the point estimate did support a treatment effect. The effects of eplerenone were seen only in patients who had signs (especially lung congestion) of CHF at the time of entry into the study. Diabetics without symptoms, even with depressed ejection fractions, had no hint of benefit from eplerenone. As this was a patient population targeted for enrollment in the trial, and bear reflecting in the label.

CHEMISTRY

The Chemistry reviewer identified no deficiencies. The waiver for the environmental assessment was submitted and found acceptable.

PRE-CLINICAL PHARMACOLOGY TOXICOLOGY

No new toxicology studies were submitted. Several pharmacology studies, looking at the effects of eplerenone in models of heart failure were submitted. Eplerenone had some effects to reduce collage formation in the hearts of such animals, and improved ejection fractions in a mouse model of CHF and in a rat post-MI CHF model, when compared with control treatment. Comparisons with enalapril were less striking, with enalapril apparently better in some studies, with modest additive effects on outcomes suggested in others. Some studies on excretion, including a study on biliary excretion, add little to what was previously known.

3

The reviewer made one recommendation regarding the removal of some descriptive language proposed by the sponsor; I concur with the recommendation.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Dr. Mishina reviewed a study comparing the pharmacokinetics of eplerenone in patients with CHF to healthy volunteers. She found that the C_{max} and AUC of the parent molecule, as well as the two principle metabolites, increased around 35% in the CHF patients. Because of small number of subjects (n=16 total) and wide inter-subject variability, these differences were neither statistically nor clinically significant.

The sponsor also conducted sparse sampling in the EPHEBUS trial to model the clearance of eplerenone in this population and to then compare the values with those previously obtained in normal volunteer and elderly populations. Dr. Mishina has done a nice job of summarizing the limitations of these analyses, principally limited (she thought) by the extensive data censoring done by the sponsor, resulting in lowered confidence in the results (for instance, see her page 28-29, discussing the model and its lack of validation). When compared with the geriatric population previously studied, the clearance of eplerenone obtained in EPHEBUS (4.9 L/hr) was not substantially different from the elderly population previously reported (6.6 L/hr). It was lower than the reported value for normal volunteers (10.8 L/hr)

MEDICAL/STATISTICAL REVIEW

Efficacy

The two reviews by Dr. Marciniak and Dr. Hung elegantly and critically evaluate the safety and efficacy of EPHEBUS. Dr. Marciniak has additionally summarized the results of the RALES trial, using aldactone. I'll make a few comments to elaborate on some of the issues identified in the summary above.

Hospitalizations

The first point to make is that the sponsor chose to emphasize a somewhat arbitrary definition of CV hospitalization in their primary endpoint, one that excluded a large fraction of events that a typical physician would understand as 'cardiovascular' in nature. When a more representative fraction of cardiovascular hospitalizations is included in a post-hoc analysis, the p-value favoring eplerenone becomes much less convincing (around 0.30 unadjusted), a p-value that is higher than the 0.01 the sponsor allocated to the combined CV death/hospitalization endpoint. ¶

¶ It is also true, somewhat paradoxically, that the size of the treatment effect on hospitalizations is less mortality (around 8% versus 13%). This could be explainable if, as suggested by Dr. Marciniak, the primary effects of eplerenone on mortality are to prevent arrhythmic deaths related to potassium, while a separate mechanism affects the incidence of hospitalizations, a mechanism not elucidated in this trial. In support of an effect on hospitalizations, it seems relevant to look at the effects of other related molecules. In the RALES trial, aldactone also reduced hospitalizations in a slightly different population of patients with CHF, in addition to a robust effect on mortality (table 72 of medical review). Working against an effect on hospitalizations, however, is the absence of any symptom benefits for eplerenone in EPHEBUS using the Kansas City Cardiomyopathy Questionnaire (section 3.4.2.2.5 in the Medical Review). I am also not convinced by the data on the changes in the NYHA class (table 27), despite the statistically significant differences seen. As pointed out by Dr. Marciniak, a large fraction of the assignment to 'worsened' NYHA class was driven by the excess deaths in the placebo group.

Overall, then, we have one trial suggesting that eplerenone use causes a small reduction in hospitalizations, with no internal supportive data. The difference between the two treatment groups in the trial is not overwhelming. We also have supportive data from a trial in a related population with a related drug. In the end, then, additional trial data are needed. ¶

Sub-Group Analyses

The sponsor and the reviewers have conducted a series of analyses looking at various sub-groups. ¶

¶ Which bear mention in addition to the plot? First, the sponsor focused on the diabetic without signs of CHF as a population of particular interest. The results in that population were not simply neutral, but instead had a point estimate that was adverse for eplerenone (with confidence intervals that overlapped unity). Additional mention of such a sub-set finding seems appropriate. For one other sub-set, patients over the age of 75, the data are also consistent with a loss of treatment benefit for eplerenone (actually, the data seem best fitted to a continuous function, the 75 year cut-off is arbitrary, see section 3.4.2.3.3 in Dr. Marciniak's review for discussion). That this subset finding could be chance, however, is supported by the opposite results seen for aldactone in the RALES trial (section 4.4.2.3.3, table 77), where patients >75 benefited quite nicely from mineralocorticoid receptor blockade. The other subsets of interest, per the CFR, should be reflected in label, including the small number of Blacks. Other demographic subset analyses discussed by the sponsor and the reviewers (use of beta-blockers, hx of hypertension) seem best left to the box and whisker plot.

The effects of eplerenone in various geographic regions were also examined (Dr. Marciniak's review, table 28). Here, as in other multi-national trials, the effect varied by region. The U.S. results didn't differ significantly from the overall effect, but in Canada the use of eplerenone was nominally disadvantageous to placebo. Latin American seemed a particular outlier (absolute treatment difference of almost 8% favoring eplerenone). The Agency continues to struggle with how to interpret these regional variations; this study will only add additional data for that discussion.

Safety

Dr. Marciniak has reviewed the safety, and the reader is referred there for details. No novel safety concerns were identified in EPHEBUS. The incidence of hyperkalemia continues to be the primary safety concern, and the same populations who were at increased risk for hyperkalemia in the hypertension development plan continue to be at risk in the CHF program: diabetics with proteinuria, patients with impaired renal function (see section 4.3.4.6.1 of his

review). Patients taking an ACE-I, ARB also were at increased risk for hyperkalemia. The rates of sex hormone related adverse events were low, and are similar to those reported in the hypertension development program (see his section 3.4.3.6.2). Finally, he makes some interesting observations about the use of eplerenone and decreased numbers of reported prostate cancers (table 62). I also seem to remember data on eplerenone being a 5-alpha reductase inhibitor, which would provide a potential mechanism for such effects. Without longer-term prospective data, it is provocative but not established.

SUMMARY

The EPHEBUS trial of eplerenone, reinforced by the data on aldactone in the RALES trial, provides a robust demonstration of eplerenone's effects to reduce mortality in patients with CHF after myocardial infarction. A less convincing effect of eplerenone on hospitalization was suggested. No demonstrated effects of eplerenone on other measures of benefit (*e.g.*, symptoms) were shown. The trial identified no novel safety concerns for the patients with CHF, and the use of the product, like its use in hypertension, will likely be limited to some extent by the development of hyperkalemia. Approval of this supplement will make a novel class of agents in the treatment of CHF available to patients, and this trial represents an important advance in therapy.

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/s/

Doug Throckmorton
10/6/03 03:42:05 PM
MEDICAL OFFICER

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**Amendment to Pending Supplemental
Application S-002: Response to FDA Request**

22 August 2003

Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation & Research
Food and Drug Administration
Woodmont II (HFD-110)
1451 Rockville Pike
Rockville, Maryland 20852

RE: sNDA 21-437
INSPRA™
(eplerenone)

Dear Dr. Throckmorton:

In response to an e-mail request from Dr. Nallaperum Chidambaram, concerning S-002, enclosed you will find an Environmental Assessment, Claim for Categorical Exclusion.

This amendment is being provided electronically and is formatted in accordance with FDA Guidance: "Guidance for Industry Providing Regulatory Submissions in Electronic Format – General Considerations" (January 1999, IT 2) and "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs" (January 1999, IT3). The submission is provided on 3.5 inch Floppy Disk comprising less than 1MB. This submission has been verified free of any virus using Trend OfficeScan WinNT, version 5.02.

Please direct any questions or concerns to the undersigned.

Sincerely,

 *Lynne E. Weissberger* for:

Lynne E. Weissberger, Ph.D.
Associate Director, Global
Regulatory Affairs
Tel: (847) 982-7469
FAX: (847) 982-8090

ENVIRONMENTAL ASSESSMENT

**INSPRA™ Tablets
Supplement (S-002) to NDA 21-437**

Claim for Categorical Exclusion According to 21 CFR 25.15 (a) and (d)

G.D. Searle, LLC, a wholly owned subsidiary of Pfizer Inc, claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR 25.31 (b) applicable for action on a supplement to an NDA when the estimated concentration of drug substance at the point of entry into the aquatic environment will be below 1 part per billion. Pfizer Inc claims that to our knowledge, no extraordinary circumstances exist.

Preparers:

Lisa A. Constantine, Senior Chemical Safety and Control Coordinator, Environmental Sciences, Chemical Research and Development, Groton Laboratories, Pfizer Global Research and Development. BS in Chemistry, MBA, Certified Industrial Hygienist with 19 years experience in EH&S, including 5 years with Chemical Research and Development.

Richard T. Williams, Ph.D., Assistant Director, Environmental Sciences, Chemical Research and Development, Groton Laboratories, Pfizer Global Research and Development. Ph.D. in Microbiology / Ecology with 20 years of experience in environmental science, including 11 years experience within Chemical Research and Development.

The undersigned states that (1) the action requested qualifies for a categorical exclusion and meets categorical exclusion criteria 21 CFR 25.31 (b) and (2) to Pfizer Inc's knowledge, no extraordinary circumstance exist.

Richard T. Williams, Ph.D.

Assistant Director
Environmental Sciences
Chemical Research and Development
Pfizer Global Research and Development
Groton, CT 06340


Signature

20 August 2003
Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-437/S-002

G.D. Searle LLC
Attention: Lynne E. Weissberger, Ph.D.
4901 Searle Parkway
Skokie, IL 60077

Dear Dr. Weissberger:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Inspra (Eplerenone) 25, 50, and 100 mg Tablets

NDA Number: 21-437

Supplement number: 002

Review Priority Classification: Priority (P)

Date of supplement: April 4, 2003

Date of receipt: April 7, 2003

This supplemental application proposes the use of Inspra to \square

J

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 6, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 7, 2003.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Room 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Room 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any question, please call:

Mr. Daryl Allis
Regulatory Project Manager
(301) 594-5309

Sincerely,

{See appended  electronic signature page}

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Zelda McDonald
4/16/03 04:30:50 PM

sNDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-437 Supplement # S-002 SE1

Trade Name: Inspra
Generic Name: eplerenone
Strengths: 25, 50 & 100 mg Tablets

Applicant: G.D. Searle LLC

Date of Application: April 4, 2003
Date of Receipt: April 7, 2003
Date of Filing Meeting: May 22, 2003
Filing Date: June 6, 2003
74-day Letter Date: June 20, 2003
User Fee Goal Date: October 7, 2003

Indication(s) requested: [

]

Type of Application: (b)(1) Supplement NDA 21-437/ S-002

Therapeutic Classification: P
Chemical Classification: (1,2,3 etc.): SE1
Other (orphan, OTC, etc.): No

User Fee Status: Paid

Form 3397 (User Fee Cover Sheet): YES
User Fee ID # 4525

Clinical data? YES

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application? YES

If yes, explain:

Inspra was approved for the treatment of hypertension on September 27, 2003. The sponsor was granted 5 years of exclusivity for a NME.

Does another drug have orphan drug exclusivity for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A

Is the application affected by the Application Integrity Policy (AIP)? NO

If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES
- Was the Form 356h included with an authorized signature? YES
- Is the Submission complete as required under 21 CFR 314.50? YES
- If an electronic NDA, does it follow the Guidance? YES

If an electronic NDA, all certifications must be in paper and require a signature. YES
Which parts of the application were submitted in electronic format?

The entire sNDA is electronic with paper review copies of Modules of 1, 2, and 3.

Additional comments:

- If in Common Technical Document format, does it follow the guidance? YES

- Is it an electronic CTD? YES

If an electronic CTD, all certifications must be in paper and require a signature. YES
Which parts of the application were submitted in electronic format?

Entire sNDA is electronic with paper copies of Modules of 1, 2, and 3

Additional comments:

- Patent information included with authorized signature? YES

- Exclusivity requested? YES; 3 years
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES

- Financial Disclosure information included with authorized signature? YES
(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A
Not necessary; no inspections will be required

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
- Drug name/Applicant name correct in COMIS? YES
- List referenced IND numbers: IND 51,780 and NDA 21-437
- End-of-Phase 2 Meeting(s)? Date April 27, 1999 YES
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date January 9, 2003 YES
If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? (In EDR, E-mail sent to Dr. Haffer) YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? (in EDR, E-mail sent to Ms. Birdsong) YES
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
If no, did applicant submit a complete environmental assessment? N/A
If EA submitted, consulted to Nancy Sager (HFD-357)? N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? NA
- If parenteral product, consulted to Microbiology Team (HFD-805)? N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 22, 2003

BACKGROUND:

Inspira (eplerenone) (NDA 21-437) was approved for the treatment of hypertension as monotherapy or in combination with other anti-hypertensive agents on September 27, 2002. This supplemental new drug application provides data in support for a new indication

The pivotal eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS) was designed to measure two co-primary endpoints (all-cause mortality and time to first occurrence of cardiovascular mortality or cardiovascular hospitalization).

This sNDA is referencing the original NDA for the Chemistry, Manufacturing and Controls and pharmacology/toxicology information. The sponsor, to date, has not marketed Inspira for the treatment of hypertension. In addition, there was a recent change in ownership from G.D. Searle LLC (Pharmacia) to Pfizer, Inc., however, the sponsor, to date, has not submitted documentation officially notifying the Agency of this change in sponsor.

ATTENDEES:

Douglas C. Throckmorton, M.D.	Director, Division Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Deputy Director, HFD-110
Thomas Marciniak, M.D.	Medical Officer, HFD-110
Elena Mishina, Ph.D.	Biopharmaceutist, HFD-860
James Hung, Ph.D.	Team Leader, Statistician, HFD-710
Nallaperum Chidambaram, Ph.D.	Chemist, HFD-810
Albert DeFelice, Ph.D.	Team Leader, Pharmacologist, HFD-110
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
Robert Shibuya, Ph.D.	Pharmacologist, DSI, HFD-45
Edward Fromm, R.Ph.	Acting Chief, Project Management Staff, HFD-110
Daryl Allis, M.S., F.N.P.	Project Manager, HFD-110

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>	<u>Completion Date</u>
Medical:	Dr. Marcinick	August 1, 2003
Secondary Medical:	N/A	
Statistical:	Dr. Hung	August 1, 2003
Pharmacology:	Dr. Hausner	August 1, 2003
Statistical Pharmacology:	N/A	
Chemist:	Dr. Chidambaram	August 1, 2003
Environmental Assessment (if needed):	N/A	
Clinical Pharmacology:	Dr. Mishina	August 1, 2003
DSI:	N/A	
Regulatory Project Manager:	Mr. Allis	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL	FILE <u> X </u>	REFUSE TO FILE _____	
• Clinical site inspection needed:			NO
• Advisory Committee Meeting needed?	date if known; _____		To be Determined
CLINICAL MICROBIOLOGY	FILE _____	REFUSE TO FILE _____	N/A
STATISTICS	FILE <u> X </u>	REFUSE TO FILE _____	
BIOPHARMACEUTICS	FILE <u> X </u>	REFUSE TO FILE _____	
• Biopharm. inspection needed:			NO
PHARMACOLOGY	FILE <u> X </u>	REFUSE TO FILE _____	
• GLP inspection needed:			NO
CHEMISTRY	FILE <u> X </u>	REFUSE TO FILE _____	
• Establishment(s) ready for inspection?			NA
• Microbiology			NO

ELECTRONIC SUBMISSION: YES
Any comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

X No filing issues have been identified.

_____ Filing issues to be communicated by Day 74.

ACTION ITEMS:

- Filing issues/no filing issues will be documented and conveyed to applicant in the 74-Day letter by June 20, 2003.

Mr. Daryl Allis
Regulatory Project Manager, HFD-110

Draft:	05/23/03	Final	06/02/03
RD			
Shibuya	05/23/03		
Chidambaram	05/23/03		
Hausner	05/28/03		
Hung	05/28/03		
Mishnia	05/28/03		
Marciniak	05/28/03		
Stockbridge	05/29/03		
Fromm	05/29/03		
Throckmorton	05/30/03		

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daryl L. Allis
6/2/03 10:29:47 AM

Minutes of a Meeting

Meeting Date: January 9, 2003
Type of Meeting: B, Pre-sNDA
NDA Application: 21-437 Inspra (eplerenone)
IND Application: 51,780 eplerenone
Sponsor: G.D. Searle LLC
Meeting Request Date: November 8, 2002
Confirmation Date: November 19, 2002
Briefing Package Received: December 19, 2002

Meeting Chair: Douglas C. Throckmorton, M.D.
Meeting Recorder: Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton, M.D. Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D. Team Leader, Medical Officer, HFD-110
Abraham Karkowsky, M.D., Ph.D. Team Leader, Medical, HFD-110
Thomas Marciniak, M.D. Medical Officer, HFD-110
James Hung, Ph.D. Team Leader, Statistician, HFD-710
John Lawrence, Ph.D. Statistician, HFD-710
Patrick Marroum, Ph.D. Team Leader, Biopharmaceutics, HFD-860
Daryl Allis, M.S., F.N.P. Regulatory Health Project Manager, HFD-110

G.D. Searle LLC

Richard Bittman, Ph.D. Director, CV and Non-Clinical Statistics
Anthony Coniglio, Pharm.D. Executive Director, Global CV Products
James Ferry, Ph.D. Regional Sr. Director, Clinical Pharmacology
Donald Raineri, Pharm.D. Director, Global Regulatory Affairs
Ronald Garutti, M.D. Vice President, Global Regulatory Affairs
Jay Kleiman, M.D., M.P.A. Medical Director, CV and Metabolic Diseases Clinical Research
Susan Garthwaite, Ph.D. Global Project Leader, Senior Director, Project Development
Marjorie Gatlin, M.D. Senior Director, CV and Metabolic Diseases Clinical Research
Weizhong He, Ph.D. Statistical Scientist, Statistics and Programming
Robert Kowalski, Pharm.D. Senior Director, Global Regulatory Affairs
Myrlene Staten, M.D. Vice President, CV and Metabolic Diseases Clinical Research
Lynne Weissberger, Ph.D. Associate Director, Global Regulatory Affairs

Background

Inspira (eplerenone) (NDA 21-437) is a selective aldosterone blocker that was approved for the treatment of hypertension on September 27, 2002. The sponsor is preparing to submit a supplemental NDA (sNDA) that will include safety and efficacy data to support the use of eplerenone for the reduction of mortality and morbidity in patients with heart failure after myocardial infarction. An End-of Phase 2 meeting to discuss the eplerenone heart failure program was conducted on April 20, 1999.

Discussion Points

The sponsor presented an overview of the results from the Eplerenone's Heart Failure Efficacy and Survival Study (EPHESUS).

Organization of the Supplemental NDA

The sponsor proposes the following:

- Electronic submission for the supplemental NDA in the ICH Common Technical Document Format
 - Providing paper review copies of Modules 1 & 2 only
 - Cross reference the pre-clinical studies and Chemistry, Manufacturing and Controls data to the Inspira (eplerenone) NDA 21-437
 - Cross reference NDA 21-437 for the clinical pharmacology information regarding metabolism, drug-drug interactions and the influence of renal failure and hepatic failure on eplerenone pharmacokinetics
 - The Randomized Aldactone Evaluation Study (RALES) manuscript, final study report, blank case report forms annotated with SAS data sets and the RALES data will be submitted as a second trial that supports the concept that aldosterone blockade reduces mortality in patients with heart failure
- The Division agrees that the proposed organization of the sNDA is acceptable.

ISE/Clinical Summary

The sponsor proposes to prepare a Clinical Summary (Module 2.7) that will encompass information expected to represent the Integrated Summary of Efficacy (ISE) in lieu of an independent ISE. This document will be supported by the information contained in Module 5.

- The Division agrees that the proposed Clinical Summary is acceptable.

ISS/Clinical Summary

The sponsor proposes to prepare a Clinical Summary (Module 2.7) that will encompass information expected to represent the Integrated Summary of Safety (ISS) in lieu of a separate ISS. In addition to the standard safety analyses, the following have been identified as safety events of special interest: hyperkalemia, hyperuricemia, sex hormone mediated events such as gynecomastia and menstrual disorders and new onset diabetes mellitus. They plan to discuss the events of special interest individually. They also plan to present in detail patients identified as lost to follow-up and the methods for attempting to locate patients.

- The Division agrees that the proposed Clinical Summary is acceptable.
- The Division suggests the sponsor consider the following:
 - Break out the events of special interest to include gynecomastia, gynecomastia and thyroid events
 - Provide the extent of follow-up for non-mortal endpoints
 - All events are adjudicated
 - Submit case report forms for each patient
- The sponsor agrees to provide case report forms as requested.

Prescribing Information

The sponsor proposes a combined hypertension and heart failure label [

]

- The Division agrees that a combined label is acceptable: []
- The Division suggests that the sponsor look at other labels for drugs that have been approved for HTN and heart failure post-myocardial infarction.

Clinical Trial(s) for Approval

There was a discussion regarding the number of trials needed for approval. The sponsor asked if the data they presented today (EPHESUS study) held up to review, would this support an approval as a single trial separate from the RALES data.

- Dr. Throckmorton explained that on the surface the data are robust; however, we can not comment on the approval prior to reviewing the data. In addition, the Advisory Committee has agreed that prior data may be supportive in understanding the drug in context but p values are not attached. The data from RALES potentially plays this role.
- Dr. Karkowsky stated that the patient population for RALES and EPHESUS studies are different (RALES used "sick" CHF patients and EPHESUS used post-MI patients), therefore, the EPHESUS trial needs to stand on its self.
- Dr. Marciniak requested that the sponsor submit the following with the sNDA:
 - Concurrent cardiovascular medications by generic name and class, by patient per week or month
 - Minutes from the DSMB
 - Minutes from the endpoint committee

Advisory Committee

The sponsor asked if these data would be presented to the Cardio-Renal Advisory Committee.

- Dr. Throckmorton stated that the Division likes to take trials with important public health issues to the Advisory Committee, but it might depend on the timing of the submission and the Advisory Committee schedule.

[

- [] but will defer a final decision until the data are submitted to the Agency.

[

The Division noted that the sponsor was granted a deferral for pediatric studies with eplerenone for the treatment of hypertension. []

]

• []

J

Statistical Data

There was a discussion regarding submission of the statistical data for the sNDA.

- Dr. Hung suggests the sponsor agrees to provide the following:
 - SAS transport files
 - SAS code used to generate the analysis data from the raw data
 - SAS files for the raw data
 - Annotated Case Report Form identifying the SAS file abbreviations

Conclusions/ Recommendations

- The proposed organizational plan for the sNDA is acceptable.
- The sponsor plans on submitting the sNDA in mid-April 2003 to include the data from the EPHEBUS and the RALES studies.
- The Division suggests that the sponsor prepare for the Advisory Committee.
- The sponsor is [] J
- The determination [] J can not be made at this time.

Signature recorder:

/S/ 1-27-03

Daryl Allis, M.S., F.N.P.

Concurrence, Chair:

/S/ 1-27-03

Douglas C. Throckmorton, M.D.

Draft:	01/24/03	Final:	01/27/03
RD:			
Marroum	01/24/03		
Lawrence	01/24/03		
Hung	01/24/03		
Marciniak	01/24/03		
Karkowsky	01/24/03		
Stockbridge	01/27/03		
Throckmorton	01/27/03		

MEETING MINUTES

APR 27 1999

Date: April 20, 1999

Subj: IND 51,780 Eplerenone Oral for CHF
End of Phase 2 Meeting

Sponsor: Searle

4901 Searle Parkway
Skokie, IL 60077

Meeting Chair: Robert Temple, M.D.
Recorder: Gary Buehler
Sponsor Lead: John Alexander, M.D.

Attending:

Searle

John Alexander, M.D.	Executive VP, Clinical Research
Barbara Roniker, M.D.	Senior Director, Clinical Research
Jay Kleinman, M.D.	Director, Clinical Research
Susan Garthwaite	Sr. Project Director, Project Management
Donald Raineri, Pharm.D.	Director, Regulatory Affairs
Richard Bittman, Ph.D.	Director, Statistics
Ingrid Hoos	Manager, Regulatory Affairs

Searle Consultants

Bertram Pitt, M.D. Prof. Of int. Med., U. of Michigan School of Med.

FDA

Robert Temple, M.D.	Director, Office of New Drug Eval. I, HFD-101
Robert R. Fenichel, M.D., Ph.D.	Deputy Dir., Div. Of Cardio-Renal Drug Prod, HFD-110
Charles Ganley, M.D.	Medical Team Leader, HFD-110
Juan Carlos Pelayo, M.D.	Medical Reviewer, HFD-110
Aleka Kapatou, Ph.D.	Statistical Reviewer, HFD-710
Gabriel Robbie, Ph.D.	Clinical Pharmacology Reviewer, HFD-810
Gary Buehler	Project Manager, HFD-110

BACKGROUND

Eplerenone is a highly selective aldosterone receptor antagonist. It is a steroid nucleus-based antimineralcorticoid which effectively blocks aldosterone at receptor sites in tissues throughout the body. The compound is presently under development for hypertension. Searle asked to meet to discuss their phase 3 program for congestive heart failure.

DISCUSSION

Division reviewers and Dr. Temple reviewed the firm's pre-meeting package, and it was discussed immediately before the meeting. The firm's overall plan was considered acceptable. The following points were clarified at the meeting:

1. Entrance Criteria

Dr. Pitt said that patients post-MI with evidence or history of heart failure and ejection fraction ≤ 35 could be entered into the trial. These patients could have received various usual care medications including

thrombolytics, ACE inhibitors, beta blockers and/or aspirin. Patients with heart failure of primary valvular or congenital etiology, cardiogenic shock, unstable angina, creatinine > 2.5 mg/dl, potassium > 5 mEq/dl or systolic BP < 90 will be excluded.

Usual Care

The firm said that they will recommend that all patients be on ACE inhibitors and that patients can also be on beta blockers, lipid lowering agents and diuretics.

Ability to Ethically Conduct the Trial

There was concern that, in light of the positive result seen in the RALES trial, it would not be ethically possible to conduct another placebo controlled trial in CHF patients with this type of drug. Dr. Pitt presented the results of the RALES trial. From his presentation, it was clear that the proposed patient population to be studied in the eplerenone trial differed significantly from that studied in RALES. RALES studied predominately NYHA class IV patients with some class IIIs being entered. These patients also did not have to have had a previous MI. The eplerenone trial will study NYHA class II and III patients who have had a recent MI.

Hyperkalemia

Hyperkalemia was a frequently seen adverse effect in the RALES trial and in the initial trials with eplerenone. The firm said that there were some problems with hyperkalemia at the 100 mg dose. To address this, they have instituted strict guidelines relating to dose escalation based on serum potassium levels. All patients will be given 25 mg daily to start. If there is no evidence of hyperkalemia, the patient's dose will be increased to 50 mg daily. If there is evidence of hyperkalemia, the dose can be decreased to 25 mg every other day. If, after 8 weeks, the patient still has rales and signs of progressing heart failure, the dose can be increased again to 100 mg daily. These patients, however, cannot have hyperkalemia. The firm was advised to have specific guidelines for increasing the dose to 100 mg.

The firm said that they have not had a problem with patients getting into trouble with hyperkalemia. They plan to monitor the patients throughout the trial for this problem.

Single Trial

The firm plans to complete one trial with a target p value of 0.05. Dr. Temple said that when only one trial is submitted in support of an application, we would need to see convincing results to support approval. We hesitate to state exactly how convincing, but it would certainly need a p value lower than 0.05. Some support for the concept that this kind of drug could be effective in CHF could be provided by the RALES study. The sponsor was advised to submit the RALES trial in support of this trial.

Renal Failure

Judging from the pre-meeting package, it appeared that there were a significant number of patients who had "renal failure" during the initial trials with eplerenone. The firm said that they had not seen a large amount of renal failure, and thought that the figures reflected an increase in BUN rather than renal failure. The Agency reviewers request that the number of patients whose creatinine changed by 0.5 be submitted for review.

Stopping Rules

The firm was advised to have very conservative stopping rules for the trial to preserve the ability to achieve a convincing result. Dr. Temple said that they will have nothing to support their trial but the RALES trial, and this is somewhat of a stretch since it is with a different drug. The results of their secondary endpoints will help, but they should try to obtain as convincing result as possible.

Minutes taken by: /S/

4/27/99

Gary Buehler

Concurrence, Chair: /S/

Robert Temple, M.D.

Orig IND

HFD-110

HFD-110 GBuehler

HFD-110 SBenton

RD:	JPelayo	4/21/99
	CGanley	4/21/99
	AKapatou	4/22/99
	GRobbie	4/23/99
	RTemple	4/26/99