CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-437

Administrative Documents

PATENT STATEMENT UNDER 21 USC 355(b)(1)

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name:
- Active Ingredient(s): Eplerenone
- Strength(s): 25 mg; 50 mg; 100 mg
- Dosage Form: tablet
- Approval Date: yet to be determined

Drug Substance (Ingredient) Patent

The following U.S. Patent contains claims directed to the drug substance eplerenone:

Patent No.	Owner	Title	Expiration
4,559,332	Novartis Pharmaceuticals Corporation (formerly Ciba Geigy Corporation) Eplerenone and related patent rights licensed to Pharmacia Corporation	20-Spiroxanes And Analogues Having An Open Ring E, Processes For Their Manufacture, And Pharmaceutical Preparations Thereof	April 9, 2004 (subject to any patent term extension available under 35 U.S.C. §156 upon approval of the present New Drug Application)

The undersigned declares that the above patent covers the drug substance eplerenone, which is the subject of this application for which approval is being sought.

Drug Product (Formulation and Composition) Patent

The following U.S. Patent contains claims directed to formulations and compositions of the drug substance eplerenone:

Patent No.	Owner	Title	Expiration
4,559,332	Novartis Pharmaceuticals Corporation (formerly Ciba Geigy Corporation) Eplerenone and related patent rights licensed to Pharmacia Corporation	20-Spiroxanes And Analogues Having An Open Ring E, Processes For Their Manufacture, And Pharmaceutical Preparations Thereof	April 9, 2004 (subject to any patent term extension available under 35 U.S.C. §156 upon approval of the present New Drug Application)

Method of Use Patent

The following U.S. Patent contains claims directed to the method of use of the drug substance eplerenone:

Patent No.	Owner	Title	Expiration
4,559,332	Novartis Pharmaceuticals Corporation (formerly Ciba Geigy Corporation) Eplerenone and related patent rights licensed to Pharmacia Corporation	20-Spiroxanes And Analogues Having An Open Ring E, Processes For Their Manufacture, And Pharmaceutical Preparations Thereof	April 9, 2004 (subject to any patent term extension available under 35 U.S.C. §156 upon approval of the present New Drug Application)

The undersigned declares that Patent No. 4,559,332 covers the formulation, composition and/or method of use of the drug substance eplerenone, which is the subject of this application for which approval is being sought. In the opinion and to the best knowledge of the undersigned, there are no patents other than the Drug Substance Patent (above) that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Carl W. Battle
Vice President and Associate General Counsel
Global Intellectual Property

EXCLUSIVITY SUMMARY FOR NDA # 21-437 SUPPL # 000

Trade Name: Inspra **Generic Name:** Eplerenone

Sponsor: G.D. Searle, LLC **HFD # :** 110

Approval Date If Known: September 27, 2002

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 /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

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

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 /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 5 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 /___/ NO /_X__/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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

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

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

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

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

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:

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

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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 /___/ ! NO /___/ Explain: _____

Investigation #2 !

IND # _____ YES /___/ ! 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 /___/

If yes, explain: _____

_____

_____ _____

Signature Date

Title:

_____ _____

Signature of Office/ Date

Division Director

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/

Robert Temple

9/27/02 04:55:31 PM

CLAIMED PRODUCT EXCLUSIVITY UNDER 21 USC 355(c)(3)(D)(ii)

The Applicant, Pharmacia Corporation, is claiming exclusivity under 21 CFR 314.108(b)(2) for the drug containing the active moiety, eplerenone, which is the subject of the present application.

21 CFR 314.50(j)(3) Assertion

To the best of the Applicant's knowledge or belief, a drug containing eplerenone as the active moiety, which is the subject of the present application, has not previously been approved under Section 505(b) of the Act.

Carl W. Battle, Esq.
Vice President and Associate General Counsel
Global Intellectual Property

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

A/BLA # : NDA 21-431 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: November 29, 2001 **Action Date:** September 29, 2002

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

Applicant: G.D. Searle LLC **Therapeutic Class:** Diuretic

Indication(s) previously approved: Not Applicable; New Medical Entity

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

Number of indications for this application(s): Not Applicable; Granted deferral

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:** _____

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.** <1 **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.** 16 **Tanner Stage**____

Reason(s) for deferral:

X Adult studies ready for approval

Other: Granted in the Pre-NDA meeting on July 19, 2001 (IND [redacted]

Date studies are due (mm/dd/yy): August 17, 2004

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, /S/ ; 8/26/02

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

DEBARMENT STATEMENT

Pursuant to section 306 (k)(1) 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) [section 306(a) or (b)] in connection with this application.

Richard Shubart
Senior Director
Global R&D Quality Assurance

MEMORANDUM

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

DATE: September 27, 2002

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Eplerenone

TO: Director, Division of Cardio-Renal Drug Products, HFD-110

There are, I think, two major issues: (1) dose regimen (o.d., b.i.d.) and dose; and (2) risk of hyperkalemia and how to minimize it. My underlying assumption here is that we have no reason to think eplerenone is anything but a garden-variety antihypertensive of ordinary effectiveness; i.e., there is no reason to accept increased risk compared to alternative agents. The sponsor seems to at least partly agree, as the 400 mg o.d. dose, seemingly considerably superior to any other o.d. regimen, is not recommended because of an excess rate of hyperkalemia (K > 5.5 mcg/L).

I. Dose-response

The D/R results from all relevant studies (principally 2 studies, 010 and 049) are shown in Dr. Karkowsky's figures 2 and 3 and the following table.

Table 1
(from Marceniak Tables 3, 4)

	Plbo-subtracted (S/D), adjusted		
	Study 010		Study 049
Total Dose (mg)	o.d.	b.i.d.	o.d.
25	—	—	5.7/2.0
50	6.0/3.4	9.6/3.3	6.7/2.9
100	9.5/3.3	13.3/6.7	10.4/4.6
200	—	—	8.8/3.4
400	16.6/7.6	16.4/7.8	—

In these reasonably-sized studies (50/group for 010 and 87-88 for 049), there does seem to be a dose-response overall, but it is fairly flat and there is no evidence from actual data (as opposed to models) that 200 mg is superior to 100 mg. This was studied directly in study 049, quite a good-sized trial; 200 mg is barely better than 50 mg). It is also clear that, over the range of 50-200 mg, b.i.d. dosing is superior. The differences were significant for some comparisons, but I am sure a pooled analysis would show a significant difference, even if each dosing group does not. The ABPM data in study 049 may show some advantage of 200 mg o.d. over 100 mg o.d. for systolic BP (about 1-2 mm Hg), but not for DBP and in study 010 the b.i.d. regimens are superior for ABPM measures at both 100 and 400 mg total doses (not 50 mg). The D/R curves (Marceniak page 47) for all studies give no suggestion of a greater effect at 200 mg than 100 mg. Modeling is all well and good but it is substantially driven by a dose that will not be used (400 mg).

Other studies are not very helpful and in most cases, I don't have full data to look at. Studies 17 and 21 could perhaps suggest (in 21, but not in 017) further effect (change from baseline) going from 100 to 200 mg but that change in study 21 was no larger than the fall in BP from week 6 to 8, when dose was unchanged (I can't find numbers for the comparator, but in any case, without a placebo group, the effect size cannot be measured).

Study 015 (factorial: HCTZ 12.5, 25; eplerenone 25, 50, 200) apparently showed no significant effect of monotherapy vs. placebo so it can't contribute real dose data; it also doesn't have a 100 mg dose.

Study 020 apparently titrated to effect so that it cannot, without further analysis, contribute D/R information. Conceivably, a NONMEM analysis could generate hypotheses.

It's most regrettable that, despite our clear EOP2 warning, this 4-8 hour half-life drug was worked-up with only 150 patients given b.i.d. doses. We'll need to look closely at available K data, but we can probably take some assurance about 50 b.i.d. from the substantial number of patients on 200 o.d.

My conclusions are:

1. Eplerenone, at doses below 400 mg, is a b.i.d. drug; 50 mg b.i.d. is the most effective dose (below 400 mg) for both systolic and diastolic pressure.

2. No evidence is provided for use of doses above 100 mg. Study 049 compared 100 and 200 mg directly: 200 mg was numerically inferior. Fifty mg b.i.d. was the best treatment by cuff or ABPM by quite a bit, except for 400 mg b.i.d. in study 010.

II. Hyperkalemia (K > 5.5)

Hyperkalemia is a real risk in some patients, and the risk is plainly dose-related and patient substrate related. I do not believe we have any reason to expect uniform frequent monitoring of patients and history tells us that electrolyte problems can be very important, which is why no one recommends diuretic doses above 25 mg any more. I see no reason to use eplerenone in the higher risk populations "with monitoring" because the drug has no discernable benefit over drugs that do not require such monitoring.

I therefore believe it probably should be contraindicated in diabetics with proteinuria or patients with elevated serum creatinine. We need to look further, however, at the 100 mg dose and its effect on K^+ in these subgroups as well as in patients on ACEI's, etc.

What do we know about hyperkalemia?

1. Relevant exposure (MOR page 81): $\geq$ 1 month:

   This is hard to get from page 71 because patients show up > once in dose groups. I would say well over 600 people have had more than 1 month's exposure to 200 mg and to 100 mg.

2. Sensitive groups

   a. In study 021 (diabetes mellitus with microalbuminuria) had a 31.2% rate of K > 5.5 mEq/L, apparent in patients with Cr < 100 mL/min, i.e., a minimal decrease.

   b. In various studies, the 400 mg dose gave a hyperkalemia rate of 7.8%.

c. With minimal renal insufficiency (Cr > 1.2 mg/dl), rate of hyperkalemia was 8%, 37% on ACEI and eplerenone and 27% with ACEI alone (much higher than I recall). This needs to be looked at by dose.

We need to look at hyperkalemia rates by group and by dose. For example:

	n	n with any K > 5.5	mean change
Total population > 30 days Daily Dose = 50 mg o.d., b.i.d. 100 mg o.d. 100 mg b.i.d. 200 mg b.i.d. 400 mg o.d.; b.i.d. } = D	XXX	y	
With diabetes mellitus > 30 days D			
With diabetes mellitus and Creat > 1.2 D			
With diabetes mellitus and albuminuria D			
All Creat > 2 D			
All with ACEI D			
All with thiazide D			
Any other interesting subgroups			

/S/

Robert Temple, M.D.

cc:
HFD-101/R Behrman
HFD-101/R Temple
drafted:sb/9/23/02
final: sb/9/27/02
Filename:Eplerenone_MM_Sep02.doc

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

/s/

Robert Temple
9/27/02 04:59:31 PM
MEDICAL OFFICER

NDA ACTION LETTER ROUTING RECORD

NDA#: 21-437 Date Received: September 13, 2002

Drug: eplerenone tablets Division: HFD- 110

Type of Letter: AP AE NA Drug Classification: ___

Patent Info Received: _____ Safety Update: _____

Phase IV Commitment: _____

REVIEWER	RECEIPT	ACTION
1. Colleen LoCicero Associate Director for Regulatory Affairs	Date 9/13 Initials CLL	Date 9/16 Initials CLL

Comments: User fee goal date - 9/29/02

2. Chemistry Review	Date 9/17 Initials ~~HBP~~ HBP	Date 9/17 Initials HBP

Comments: EER is acceptable. EA is a categorical exclusion which is acceptable. All CMC deficiencies have been resolved satisfactorily. CMC recommendations/comments have been included in the action letter and the enclosed labeling (rekest & expiry dating for DS+DP and labeling. The chemical name in the Description section of PI is not the same as that in the CMC review and NDC#s for some appear to be incorrect (see notes)

3. Pharmacology & Toxicology Review - see attached	Date _____ Initials _____	Date _____ Initials _____

Comments:

3. R Behrman, M.D. Dep Director, ODEI	Date _____ Initials _____	Date _____ Initials _____

Comments:

4. R. Temple, M.D. Director, Office of Drug Evaluation I	Date _____ Initials _____	Date _____ Initials _____ Returned to Division for Corrections _____ Forwarded _____ Letter Signed _____

Comments:

Locicero, Colleen L

From: El Hage, Jeri D
Sent: Thursday, September 19, 2002 3:25 PM
To: Allis, Daryl; Hausner, Elizabeth A
Cc: Locicero, Colleen L; Benton, Sandra J
Subject: RE: Draft letter and labeling eplerenone

Daryl,

Thanks for forwarding the final labeling and approval letter for Eplerenone. The pharm/tox sections of the label look fine as written.

Jeri

-----Original Message-----
From: Allis, Daryl
Sent: Thursday, September 19, 2002 10:57 AM
To: El Hage, Jeri D
Cc: Locicero, Colleen L
Subject: Draft letter and labeling eplerenone

Attached are the latest **DRAFTS** of the letter and labeling:

<< File: Eplerenone labeling edited 3.doc >>

<< File: 21437ap.DOC >>

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA# 21-437	Efficacy Supplement Type SE-	Supplement Number	
Drug: Inspra (eplerenone) 25, 50 & 100 mg Tablets		Applicant: G.D. Searle LLC	
RPM: Mr. Daryl Allis		HFD-110	Phone # 301-594-5309
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	NME
• Other (e.g., orphan, OTC)	NA
❖ User Fee Goal Dates	September 29, 2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	NA
• OC clearance for approval	NA
❖ 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.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (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).	( ) 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, ADRA) *(indicate date of each review)*	September 12, 2002 (PM)
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) 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)	September 12, 2002
• Most recent applicant-proposed labeling	August 26, 2002
• Original applicant-proposed labeling	Yes
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	Tradename: March 25, 2002 August 6, 2002 DDMAC: September 3, 2002 DMETS: September 6, 2002 Label Mtgs: September 6, 10, 11, 16, 23, & 26 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	1 (only 1 in class)
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	September 12, 2002
• Applicant proposed	August 26, 2002
• Reviews	August 27, 2002 (CMC) September 6, 2002 (DMETS)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
Minutes of Meetings	
• EOP2 meeting (indicate date)	July 17, 1998

• Pre-NDA meeting (indicate date)	July 19, 2001 (clinical) July 31, 2001 (CMC)
• Pre-Approval Safety Conference (indicate date; approvals only)	NA, not indicated
• Other: Telecons: Justification for standard review	January 11 & 16, 2002
❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Dr. Karkowsky: September 17, 2002 Dr. Temple: September 27, 2002
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	August 23, 2002
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	April 17, 2002
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	August 26, 2002
❖ Statistical review(s) *(indicate date for each review)*	April 25, 2002
❖ Biopharmaceutical review(s) *(indicate date for each review)*	August 23, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
Clinical Inspection Review Summary (DSI)	
• Clinical studies	August 16, 2002
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	August 27, 2002 (2 reviews) September 3, 2002
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	August 27, 2002
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: August 28, 2002 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested/Pending Approval ( )Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	August 2, 2002
❖ Nonclinical inspection review summary	NA
Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	July 15, 2002
CAC/ECAC report	July 17, 2002

Allis, Daryl

To: CDER-APPROVALS
Subject: NDA 21-437 Approval Distribution list e-mail

Approval Date: September 27, 2002
NDA: 21-437
Drug: Inspra (eplerenone)
Sponsor: G.D. Searle LLC
Indication: Hypertension
Dosage: 25, 50, and 100 mg Tablets; New Molecular Entity
Application: Rx
Classification: 1,S (New Molecular Entity, Standard Review)

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS: HFD-420)

DATE RECEIVED: 8/27/02	DUE DATE: 9/17/02	ODS CONSULT #: 02-0017-2

TO:

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

THROUGH:

Daryl Allis
Project Manager, Division of Cardio-Renal Drug Products
HFD-110

PRODUCT NAME:	**NDA SPONSOR:** G.D. Searle, LLC
Inspra (Eplerenone Tablets) 25 mg, 50 mg, and 100 mg **NDA #:** 21-437	

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

SUMMARY: In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed container labels and carton labeling for "Inspra" for safety issues relating to possible medication errors.

DMETS RECOMMENDATION:
DMETS recommends implementation of the labeling revisions outlined in section II of this review to minimize potential errors with the use of this product.

/S/

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY LABELING REVIEW

DATE OF REVIEW: August 28, 2002

NDA NUMBER: 21-437

NAME OF DRUG: Inspra (Eplerenone Tablets) 25 mg, 50 mg, and 100 mg

NDA HOLDER: G.D. Searle, LLC

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110) for a safety assessment of the labeling for "Inspra".

The sponsor had submitted the proprietary name [redacted] to the Agency, which was found unacceptable by DMETS on March 25, 2002. Subsequently, on July 17, 2002, the proprietary name Inspra was reviewed and no objections were identified by DMETS. At the time of the name evaluation the labels and labeling were not available for review.

PRODUCT INFORMATION

"Inspra" contains the active ingredient eplerenone. Eplerenone selectively blocks aldosterone binding at the mineralocorticoid receptor. Aldosterone is a key hormone in the renin-angiotensin-aldosterone system, which is involved in the regulation of blood pressure and the pathophysiology of cardiovascular disease. Eplerenone is metabolized primarily through the cytochrome P450 3A4 pathway. Significant drug-drug interactions have been found with ketoconazole, erythromycin, saquinavir, verapamil, and fluconazole. Eplerenone is supplied as 25 mg, 50 mg, and 100 mg tablets. The recommended starting dose of eplerenone is 50 mg administered once a day. The dose may be increased to 100 mg if the blood pressure is not controlled. If the blood pressure is still not controlled with a 100 mg dose, a second antihypertensive agent may be added, or some patients may respond to a 200 mg dose. Patients with medical conditions such as impaired renal function, type 2 diabetes with microalbuminuria, or mild-to-moderate hepatic impairment should have their potassium levels monitored. Patients receiving potent CYP3A4 inhibitors such as ketoconazole should initiate therapy with a 25 mg dose of eplerenone. The Division has forwarded the following labeling pieces for review: Unit Dose Labels, Unit Dose Carton Labeling, and Container Labels (30's) for the following strengths, 25 mg, 50 mg, and 100 mg.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and carton labeling of Inspra, DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

The firm has submitted a package size (30's) considered to be a "unit of use" package. Please verify that the sponsor intends to market with a child-resistant closure.

B. CONTAINER LABEL (Unit Dose)

1. Increase the prominence of the established name to be at least half the size of the proprietary name.

2. We encourage the use of boxing, colors or some other means to differentiate the strengths appearing on unit dose labels. If colors are used, please use the same colors used to differentiate strengths on container labels.

C. CONTAINER LABEL (100 mg)

The yellow color used to differentiate the stength of the 100 mg container label does not afford sufficient background contrast to ensure adequate prominence. We encourage the use of a color that will improve the readability of this labeling statement.

D. CARTON LABELING (Unit Dose 100's)

Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be in a child resistant container. We offer the following as an example:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used. [NOTE: The second sentence is optional]

III. RECOMMENDATIONS:

DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

/S/

Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Charles Hoppes
9/4/02 08:16:39 AM
PHARMACIST

Alina Mahmud
9/4/02 09:10:13 AM
PHARMACIST

Carol Holquist
9/5/02 11:12:08 AM
PHARMACIST

Jerry Phillips
9/6/02 07:11:40 AM
DIRECTOR

RHPM Overview of NDA 21-437
Inspra (eplerenone) Tablets
September 4, 2002

Sponsor:	G.D. Searle LLC
Type:	1S
Receipt Date:	November 29, 2001
User Fee Goal Date:	September 29, 2002
AP Letter Issued:	September 27, 2002
Final Draft Labeling:	Received via e-mail attachment, September 27, 2002

Background

Inspra (eplerenone) is a highly selective aldosterone receptor antagonist (SARA). It is a steroid nucleus-based antimineralcorticoid 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 compound is being developed for the treatment of hypertension. The initial NDA submission includes efficacy and safety data to support the use of eplerenone for the treatment of mild-to-moderate hypertension (HTN).

Previous correspondence and meetings regarding the development of Inspra and regulatory review process include:

1. Pre-IND meeting, January 17, 1996
2. FDA CAC approval of the alternate mouse model for carcinogenesis assessment (p53 knockout mouse model) in November 1997, and dosage selection for the rat and mouse carcinogenesis studies in December 1996 and November 1998, respectively
3. EOP2 meeting for HTN on July 17, 1998
4. Pre-NDA meeting, July 19, 2001
5. Pre-NDA CMC meeting, July 31, 2001
6. Teleconference, Carcinogenicity Issues, December 20 and 21, 2001
7. Teleconference, Discuss Standard vs. Priority Review, January 11 and 16, 2002
8. Teleconference, Carcinogenicity study methods, June 10, 2002

Medical Review
In his review dated August 23, 2002, Dr Marciniak recommends that eplerenone be approved for the treatment of hypertension, alone or in combination with other agents. Two adequate and well-controlled studies have demonstrated the efficacy in reducing significantly both diastolic and systolic blood pressure in patients with essential hypertension. Eplerenone has a tolerable side effect profile similar to other approved antihypertensive agents. The major dose-limiting toxicity, hyperkalemia, can be minimized by limiting the dosage to 50 to 200 mg daily as the sponsor has recommended and by cautious use in the special populations of patients with impaired renal function or diabetics with microalbuminuria.

Special Phase 4 Studies are not recommended at this time pending the safety results from a large clinical trial that the sponsor is currently conducting

Financial Disclosure is addressed on page 42 of the medical review.

Dr. Marciniak's recommendations regarding the proposed labeling are on pages 152 to 166 of the medical review.

Secondary Medical Review
In his memo dated September 17, 2002, Dr. Karkowsky outlines the rationale for the approvability recommendation for the use of eplerenone tablets at a dose of 50 to 200 mg daily as a single dose. Higher doses may be useful in some individuals but requires more diligent monitoring of serum electrolytes. The use of divided doses may afford slightly better blood pressure effects than the once daily dose. To a large

extent, the safety profile appears qualitatively similar to the already approved aldosterone receptor inhibitor, spironolactone. Quantitative differences in rates of adverse events between spironolactone and eplerenone are likely caused by the lower therapeutic doses of eplerenone which were studied during the development program. Because of the differences in therapeutic doses of spironolactone and eplerenone employed in the development program, overall comparisons between the two drugs with regards to safety would be misleading. Edited labeling that includes the comments from the reviewers are attached to his memo.

Statistical Review
In his review dated April 25, 2002, Dr. Lawrence stated, "From the evidence in the two pivotal studies, it appears that eplerenone 50 mg QD or higher are effective at reducing SeDBP. It is unclear whether a plateau is reached in the range of doses studied (up to 400 mg QD). Twice-daily regimens were evaluated in only one study. From the evidence, including ABPM measurements, there are no apparent differences between QD doses and twice daily doses with the same total daily dose."

Pharmacology Review
In her review dated August 02, 2002, Dr. Hausner recommended approval with no additional nonclinical studies recommended. The labeling is acceptable as written.

Biopharmaceutical Review
In his review dated August 24, 2002, Dr. Robbie concluded the clinical pharmacology and biopharmaceutics section was acceptable provided the following labeling comments are addressed adequately:

- Eplerenone blood pressure lowering effect was not different when administered BID or QD. The maximum predicted reduction in trough sitting diastolic blood pressure and sitting systolic blood pressure is about 6-8% of baseline.
- The hyperforin content in marketed St. John's Wort products vary over 16-fold. In light of this variation, a higher induction in CYP 3A4 activity, resulting in significant reduction in eplerenone concentrations can be expected. Therefore, concomitant administration of St. John's Wort should be avoided in eplerenone patients.
- The sponsor's proposal to reduce the dose to 50 mg QD with moderate inhibitors of metabolism (erythromycin, verapamil, fluconazole, sanquinavir) and reduction to 25 mg QD with potent inhibitors of CYP 3A4 (ketoconazole) is acceptable.
- The pediatric pharmacokinetic study was conducted in patients between 4 years and 14 years of age only.
  - Extrapolation of eplerenone pharmacokinetics to pediatric patients less than 4 years cannot be made.
  - The pharmacodynamics of eplerenone in pediatric patients is not known.
  - Eplerenone dose was administered with applesauce in subjects <4 years of age. The relative bioavailability of eplerenone when administered with applesauce is not known. If the sponsor proposes to administer eplerenone with applesauce in pediatric patients, the sponsor will need to conduct a study to investigate the effect of applesauce on the bioavailability of eplerenone.

In addition, an in-vivo bioequivalence study waiver was granted based on the similarity of the dissolution profiles of the 25 mg, 50 mg and 100 mg clinical and commercial tablets of eplerenone. The sponsor's proposed dissolution method of USP Apparatus II (paddles) at 50 rpm and 1000 ml of 0.1 N HCl dissolution media and dissolution specification of not less that [redacted]% (Q) in 30 minutes are acceptable.

Chemistry Review
In his final review dated September 3, 2002, Dr. Chidambaram concluded this application is recommended for Approval from a chemistry, manufacturing and controls standpoint because all the deficiencies have been satisfactorily addressed and the Office of Compliance has given an overall acceptable recommendation.

The CMC deficiencies that were listed in review #1 have been addressed satisfactorily. However, the following comments regarding retest date for the drug substance, expiration date for the drug product, USAN name(s) and description section in package insert should be included in the action letter:

- A retest date of eighteen months for the drug substance and an expiration-dating period of eighteen months for the drug product will be granted based on stability data provided.
- Please change proposed name _____ _____ to be identical with the following two USAN adopted names: (1) Pregn-4-ene, 7,21-dicarboxylic acid, 9, 11-epoxy-17-hydroxy-3-oxo-, γ-lactone, methyl ester, (7α, 11α, 17α)-; (2) 9,11α-epoxy-17-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic acid, γ-lactone, methyl ester.
- We recommend that individual synthetic iron oxides be listed in the description section of package insert.

There is no recommendation for Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

DSI
In a memo dated August 13, 2002, DSI recommends that the data from Dr. Lertora's site be excluded from the analysis because it was not verifiable. The data from this site had been damaged in a hailstorm and were subsequently destroyed. The data from the other 3 sites appear acceptable for review purposes. In follow-up, the Division requested the sponsor submit a statement that the data, excluding the data from Dr. Lertora's site, submitted to the NDA are verifiable. The sponsor has requested that each investigator sign a statement that their data are verifiable. The sponsor submitted a status report for this on-going process on September 9, 2002; they will provide a final status report within the next 2 weeks. The data from Dr. Lertora's site were not included in the statistical analysis.

Pediatric Rule
The sponsor requested and was granted a deferral (Pre-NDA meeting, July 19, 2001) for pediatric studies because the product will be ready for adult use before the pediatric data will be available. The Division issued a written request for pediatric studies on August 17, 2000.

Labeling:
The sponsor submitted marked-up labeling in WORD format on August 20, 2002. The electronic submission labeling submission was submitted August 26, 2002. The text labeling submitted in WORD format is identical to the labeling submitted to the EDR on August 26, 2002. The carton and container label comments/ recommendations were communicated to the sponsor in an e-mail dated September 12, 2002. The final draft labeling text is added to the end of the approval letter dated September 27, 2002.

Advisory Committee Meeting
No meeting held.

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

Daryl Allis, RHPM

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

Discussion Points

Methods

Dr. DeFelice asked the sponsor to describe the methods they used to analyze the kidney tissue specimens in both the 2-year chronic toxicity/carcinogenicity rat study and the 2-year diet-controlled carcinogenicity rat study.

The sponsor stated that they use the same methods for both studies, as follows:

- All additional sections were prepared for the original 2-year chronic toxicity/carcinogenicity study (original 2 sections of kidney tissue and then added 10 step-sections for a total of 12 sections per animal).
- The sections for the 2-yeat diet-controlled carcinogenicity study were prepared as above.
- The sections were then blinded and randomized for each study.
- [redacted] then read all the slides in a blinded, randomized manner (>12,000 sections of kidney tissue).
- The tissue samples were separated into 2 groups: proliferative and no proliferative changes.
- The two subsets were then analyzed by a peer review team that either agreed or disagreed with the diagnosis. The slides in question were examined for concurrence utilizing a multiple head microscope; there was a 99% concordance rate with [redacted] initial diagnosis.
- A pathology working group (PWG) of 6-7 rodent pathology experts reviewed all slides with proliferative lesions in a blinded manner prior to breaking the blind.

Dr. DeFelice asked if any of the original negative rats were identified as positive when the additional step-sections were added. The sponsor stated that there were and that there is a table in Appendix 3.6 that includes all animals with proliferative diagnosis in the original and the blinded groups that were read as positive. Overall, there is an increase in both sexes and in both the treatment and control groups. The increased incidence of proliferative diagnosis, however, shows there was a decrease in the number of carcinomas (2 initial carcinomas became negative) and there was an increase in the number of benign adenomas when the additional step-sections were added in. The pathology working group concluded that the proliferative changes were strongly correlated with chronic progressive nephropathy (CPN) which is commonly seen in rats. Additionally, the sponsor stated that CPN and the incidence of hyperplastic pathology in the 2-year diet-controlled carcinogenicity study was decreased compared to the 2-year chronic toxicity/carcinogenicity rat study.

Dr. DeFelice asked if there were any isolated neoplasms without CPN. The sponsor stated that they did not find any tumors without CPN. Additionally, the sponsor indicated that they believe kidney tumors are rare and CPN is common in rats, therefore, among animals with CPN you are likely to find an increase in the number of tumors. They do not have historical data with this kidney step-section process.

Dr. DeFelice asked if the data from the blinded reads were judicated by the pathology working group. The sponsor stated that the PWG outlined the details and listed the sections that were examined. The PWG (the group of 6-7) reviewed all slides containing proliferative lesions confirmed during the peer reviews. This was done in a blinded fashion.

In addition, the peer review, prior to the PWG, reviewed all standard slides from the females of the ad lib feeding study, males with proliferative lesions, and 20% random sampling of the other males. The peer review of the restricted diet study included review of all proliferative lesions and a 20% sampling of the remaining animals of both sexes.

Minutes of a Tele-conference

Date of Meeting:	June 10, 2002
NDANumber:	21,437 (Eplerenone)
Drug Class:	Anti-hypertensive
Sponsor:	G.D. Searle LLC
Meeting Chair:	Albert DeFelice Ph.D.

Meeting Participants:

FDA

Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HDF-110
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
Ms. Roswitha Kelly, M.S.	Statistician, HFD-710
Daryl Allis, M.S.N., F.N.P.	Regulatory Health Project Manager, HFD-110

G.D. Searle LLC

Donald Raineri, Pharm.D.	Director, Global Regulatory Affairs
Art Roth, Ph.D.	Pre-clinical Statistician
Robert Kowalski, Pharm. D.	Senior Director, Global Regulatory Affairs

Background

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist (SARA). The compound is being developed for the treatment of hypertension and the reduction of morbidity and mortality in patients with heart failure post myocardial infarction.

The pre-clinical data submitted to the IND [redacted] for eplerenone revealed carcinogenicity concerns. The standard 2-year chronic toxicity/carcinogenicity rat study reported thyroid tumors that were expected. There was an increase in renal tumors in the female rat. The female rat metabolizes the drug (eplerenone) differently in that more drug is excreted unchanged in the urine of female rats and there is more nephropathy in female rats compared to male rats. Additionally, renal cell tumors were also found in two male rats in the placebo control group. There were teleconferences, between the Division and the sponsor on December 20 & 21, 2001, to discuss the carcinogenicity findings and recommend additional data that are necessary to evaluate fully the carcinogenicity issues.

The purpose for this teleconference is to clarify the methods utilized in evaluating the kidney tissue specimens and discuss the inability to read and analyze the data sets submitted to the Division.

Statistical Analysis

Ms. Kelly explained that she is unable to use our statistical program to run the data and that the data included in each of the data sets are not clear. The Division was able to run the data the sponsor submitted previously. The sponsor stated that data set 4663C included combined data from the standard and step-section slides; data set 4663S contains data from the standard slides only. The data set 4664 has one data set because there were no lesions found in the standard sections, therefore, data for the standard sections are not necessary. Ms. Kelly asked what was included in the microscopic data set. The sponsor stated that these data are other lesions, e.g., leukemia.

Ms. Kelly noted that the length of fields is different from what is listed in the Guidance and this may explain why our programs can not read the data. She stated that she would review the data again, and the sponsor agreed to send the Division new data sets that follow the Guidance exactly. Ms. Kelly requested that the sponsor send her tables that include the tumors found for weeks 0-52; 53-78; 79-91; 92-terminal sacrifice; and terminal sacrifice. She asked for the data for the number of animals with tumors for each treatment group separately, divided by the number of animals that died. The sponsor agreed.

Recommendations/Conclusions

The Division concurs with the methods utilized by the sponsor in evaluating the tissue samples for the 2-year chronic toxicity/carcinogenicity rat study and the 2-year diet- controlled carcinogenicity rat study.

The sponsor agrees to submit both the new data sets that follow the Guidance and the tables for tumors identified at the specific time points listed above.

Addendum

Ms. Kelly notified Mr. Allis on June 10, 2002, that she was able to run the data for the males and females for both of the carcinogenicity studies after removing the blank space in the study number. She requests that the sponsor still submit the tables as requested above to determine that our results are consistent with the sponsor's data. This information was conveyed to Dr. Raineri on June 11, 2002.

Meeting Recorder: /S/ 6/26/02
Daryl Allis, M.S.N., F.N.P

Concurrence, Chair: /S/ 6/26/02
Albert DeFelice, Ph.D.

cc:
HFD-110/Mathews

Draft:	06/17/02	Final: 06/26/02
Kelly	06/24/02	
Hausner	06/24/02	
DeFelice	06/26/02	

Filing Summary/ Meeting Minutes

Meeting Date:	January 24, 2002
Type of Meeting:	45-Day Filing Meeting
NDA:	21-437 Eplerenone (SC-66110)
Sponsor:	G.D. Searle LLC
Type:	1S, Anti-hypertensive Agent
Application Date:	November 28, 2001
Receipt Date:	November 29, 2001
User Fee Goal Date:	September 29, 2002
User Fee Status:	Paid
Meeting Chair:	Raymond Lipicky, M.D.
Meeting Recorder:	Daryl Allis

Attendees:

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas C. Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Gabriel Robbie, Ph.D.	Pharmacokeneticist, HFD-860
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Nallaperumal Chidambaram, Ph.D.	Chemist, HFD-810
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
John Lawrence, Ph.D.	Statistician, HFD-710
Antoine El Hage, M.D.	Medical Officer, Division of Scientific Investigations
Natalia A. Morgenstern	Chief, Project Management Staff, HFD-110
Daryl Allis, F.N.P.	Regulatory Health Project Manager, HFD-110

Submission Complete as Required Under 21 CFR 314.50?	YES
Patent Information Included?	YES
Exclusivity Requested?	YES: 5 years
Debarment Statement Included?	YES
Pediatric Rule Addressed?	Request for Pediatric Deferral
Financial Disclosure Information Included?	YES
EOP 2 and Pre-NDA Meetings	YES: Minutes attached

BACKGROUND

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist. It is a steroid nucleus-based antimineralcorticoid, and blocks aldosterone at receptor sites in tissues throughout the body, potentially antagonizing the pathological effects of inappropriate aldosterone levels while limiting side effects associated with nonspecific steroid receptor binding. The compound is being developed for the treatment of hypertension

The initial NDA submission includes efficacy and safety data to support the use of eplerenone for the treatment of mild-to-moderate hypertension (HTN).

The sponsor has requested Priority Review for this NDA. In a teleconference on January 16, 2002, the sponsor was informed that the application would receive a Standard Review.

Previous correspondence and meetings with the Division include:

1. Pre-IND meeting, January 17, 1996
2. IND . submitted on October 24, 1996
3. FDA CAC approval of the alternate mouse model for carcinogenesis assessment (p53 knockout mouse model) in November 1997, and dosage selection for the rat and mouse carcinogenesis studies in December 1996 and November 1998, respectively.
4. EOP2 meeting for HTN on July 17, 1998
5.
6. Pre-NDA meeting, July 19, 2001
7. Pre-NDA CMC meeting, July 31, 2001
8. Teleconference: Carcinogenicity Issues, December 20 and 21, 2001.
9. Teleconference: Standard vs. Priority Review, January 11 and 16, 2002.

Estimated Review Completion

DISCIPLINE	REVIEWER	DATE EXPECT REVIEW
Medical:	Dr. Marciniak	06/30/02
Sec. Medical:	Dr. Karkowsky	08/30/02
Biopharm:	Dr. Robbie	06/30/02
Pharmacology:	Dr. Hausner	08/30/02
Chemistry:	Dr. Chidamabaram	06/30/02
Env. Assessment:	N/A	
Statistics:	Dr. Lawrence	06/30/02
Microbiology:	NA	
DSI:	Dr. Shibuya	06/30/02
Project Manager:	Mr. Allis	

PHARMACOLOGY -

The pre-clinical data submitted to the IND for eplerenone revealed carcinogenicity concerns. The 6-month Transgenic Mouse study did not have any carcinogenicity issues. The standard 2-year chronic toxicity/carcinogenicity rat study reported thyroid tumors that were

expected. There was an increase in renal tumors in the female rat. The female rat metabolizes the drug (eplerenone) differently in that more drug is excreted unchanged in the urine of female rats and there is more nephropathy in female rats compared to male rats. Body burden is consistently higher for females compared to males at equivalent dosages. Additionally, renal cell tumors were also found in two male rats in the placebo control group. The sponsor has additional data from a 2-year diet controlled carcinogenicity study in rats that have not been analyzed and evaluated.

The Division has been in contact with the sponsor regarding the rat carcinogenicity issues. They have agreed to the following:

- Serial sectioning and reading of the renal tissue from the females and males from all groups in the standard 2-year chronic toxicity/carcinogenicity rat study in a blinded or coded fashion.

- Sectioning and blinded/coded histopathologic evaluation of the kidneys from the females and males from all groups in the 2-year diet-controlled rat study.

CHEMISTRY -

Did firm request categorical exclusion for environmental assessment?	YES	
EIR package transmitted?	YES	
Trade Name Review Requested?	NO;	Trade name not submitted, to date.

DSI-

Dr. Shibuya will contact Dr. Marciniak for the list of the clinical sites for investigation.

REGULATORY REQUIREMENTS/ORGANIZATION -

The electronic application, on its face, appears to be well organized. The pharmacology-toxicology section was not linked/ book marked appropriately and the tables on pages 215-245 of the clinical summary were illegible. The sponsor has resubmitted the electronic tape of the entire Section 5 for the pharmacology-toxicology data and provided a hard copy of the clinical summary tables on pages 215-245 of the clinical summary section. The application appears to be suitable for filing.

Filing Status

There were no filing issues discussed. Everyone agreed the application could be filed.

Signature recorder: /s/ 2/28/02

Concurrence, Chair: /s/ 2/28/02

Draft:	02/15/02	Final	02/28/02
RD			
Hausner	02/20/02		
Srinivasachar	02/20/02		
Chidambaram			
Robbie	02/22/02		
Lawrence	02/22/02		
Throckmorton	02/26/02		
Morgenstern	02/28/02		

Teleconference Meeting Minutes

Meeting Date:	January 16, 2002
Type of Meeting:	C, Correspondence
NDA Application:	21-437, Eplerenone (SC-66110)
Sponsor:	G.D. Searle LLC
Meeting Request Date:	January 11, 2002
Confirmation Date:	January 14, 2002
Briefing Package Received:	January 16, 2002
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas C. Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Thomas Marciniak, M.D.	Medical Officer, HFD-110
Natalia A. Morgenstern	Chief, Project Management Staff, HFD-110
Daryl Allis	Regulatory Health Project Manager, HFD-110

G.D. Searle LLC

D. Raineri, Pharm.D.	Director, Global Regulatory Affairs
T. Koestler, Ph.D.	Senior Vice President, Global Regulatory Affairs
R. Garutti, M.D.	Vice President, Global Regulatory Affairs
J. Kleiman, M.D., M.P.A.	Medical Director, Clinical Research
B. Roniker, M.D.	Senior Director, Clinical Research
S. Garthwaite, Ph.D.	Global Project Leader, Senior Director, Project Development

Background

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist. It is a steroid nucleus-based antimineralocorticoid, and blocks aldosterone at receptor sites in tissues throughout the body, potentially antagonizing the pathological effects of aldosterone while limiting side effects associated with nonspecific steroid receptor binding. The compound is being developed for the treatment of hypertension [redacted] The NDA, for the indication of hypertension, was submitted on November 28, 2001 and the Acknowledgement Letter, dated December 17, 2001, indicating a Standard Review was issued to the sponsor. In a teleconference between the Division and the sponsor on January 11, 2002, Dr. Lipicky informed the sponsor that the Division did not agree to a Priority Review. The sponsor, at the suggestion of Dr. Lipicky, requested this teleconference with Dr Temple to discuss why they believe eplerenone meets the criteria for Priority

Review. The sponsor faxed a copy of the briefing slides summarizing their position for Priority Review on January 16, 2002.

Discussion Points

Prior to the discussion focusing on Priority Review, Dr. Temple informed the sponsor that there are concerns regarding renal tumors in rats exposed to eplerenone and the sponsor needed to provide more data to resolve the carcinogenicity issues for eplerenone. The sponsor should be aware that an action date in six months may not allow sufficient time to resolve these issues and the sponsor is likely to receive a Not Approval letter. That, of course, is a consideration separate from whether the drug meets the criteria for a Priority Review. The sponsor indicated that they are actively pursuing the tumor issue and believe they can meet the six-month goal date.

Priority Review

The sponsor presented their argument in support of Priority Review status. They stated that the goals of antihypertensive therapy are as follows:

- Reduce systolic and diastolic blood pressure.

In addition, the sponsor asserts that a drug that decreases microalbuminuria is beneficial for renal protection. The sponsor believes that eplerenone has all of these desired effects.

The sponsor summarized the reasons that the Division gave for not granting Priority Review as follows:

- Eplerenone is just another antihypertensive.
- Another drug exists with the same mechanism of action.

The sponsor indicated that they believe eplerenone meets the criteria for priority review, as follows:

- Eplerenone is effective in lowering blood pressure in Blacks and Caucasians regardless of renin levels. Angiotensin Converting Enzyme Inhibitors (ACEs) and Angiotensin Receptor Blockers (ARBs) are not as effective in Blacks (low renin levels).
- Eplerenone is more effective in reducing surrogate markers of cardiovascular (CV) risk (actually microalbuminuria) than calcium channel blockers (CCBs).
- Spironolactone has the same mechanism of action, but:
  - Eplerenone's safety and tolerability is unquestionably superior.
  - There are robust blood pressure data available for eplerenone in high-risk hypertensive subpopulations (Blacks, low-renin, systolic hypertensives). Blood pressure data are limited for spironolactone.
  - Eplerenone benefits on markers of CV risk are supported by clinical data.

The sponsor also referenced the African American Study in Kidney Disease (AASK) that stopped the calcium channel blocker arm because the study drug did not stop progression of renal disease in Blacks. Additionally, they noted that there is a greater decrease in microalbuminuria with eplerenone compared to ACEs. The sponsor believes that eplerenone meets the criteria for Priority Review by addressing an unmet public health need not documented for spironolactone in the following hypertensive subpopulations:

- Blacks.
- Low renin HTN.
- Systolic HTN.

Dr. Temple stated that he agrees with the Division; Eplerenone, for the indication of HTN, does not meet the criteria for Priority Review for the following reasons:

- Eplerenone is "another" anti-hypertensive drug until distinct outcome effects are documented.

- Diuretics work well for the treatment of HTN in systolic hypertension and in Blacks; potassium sparing agents can be added if hypokalemia is a concern.
- Diuretics have been shown to reduce CV events.
- The Division has never accepted microalbuminuria as a surrogate marker for clinical benefit. It is not known if decreasing microalbuminuria, in Blacks, is beneficial for renal protection.
- Spironolactone does what eplerenone does . [redacted] The sponsor (G.D. Searle LLC) has never submitted these data.

Conclusions/ Recommendations

Given the absence of a reasonable case for superiority, safety or efficacy, when compared with other available therapies, Eplerenone (NDA 21-437) for the indication for hypertension will receive a Standard Review. The goal date is September 29, 2002.

Signature recorder: /S/ 3-5-02
Daryl Allis

Concurrence, Chair: /S/
Robert Temple, M.D.

Draft:	02/08/02	Final:	02/21/02
RD:			
Throckmorton	02/15/02		
Karkowsky	02/14/02		
Marciniak	02/08/02		
Morgenstern	02/20/02		

Teleconference Meeting Minutes

Meeting Date:	January 11, 2002
Type of Meeting:	C, Guidance
NDA Application:	21-437, Eplerenone (SC-66110)
Sponsor:	G.D. Searle LLC
Meeting Request Date:	January 4, 2002
Confirmation Date:	January 8, 2002
Briefing Package Received:	January 11, 2002
Meeting Chair:	Raymond Lipicky, M.D.
Meeting Recorder:	Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas C. Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Thomas Marciniak, M.D.	Medical Officer, HFD-110
Daryl Allis	Regulatory Health Project Manager, HFD-110

G.D. Searle & Co.

D. Raineri, Pharm.D.	Director, Global Regulatory Affairs
W. Begley	Senior Director, Global Regulatory Affairs
S. Olmstead	Executive Director, Global Regulatory Affairs
R. Garutti, M.D.	Vice President, Global Regulatory Affairs
J. Kleiman, M.D., M.P.A.	Medical Director, Clinical Research
B. Roniker, M.D.	Senior Director, Clinical Research
R. Bittman, Ph.D.	Director, Clinical Studies
S. Garthwaite, Ph.D.	Global Project Leader, Senior Director, Project Development
J. Moe	Vice President, Global Toxicology
A. Roth, Ph.D.	Fellow, Preclinical Statistics

Consultants

Background

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist (SARA). It is a steroid nucleus-based antimineralcorticoid that effectively blocks aldosterone at receptor sites in tissues throughout the body, thereby antagonizing the pathological effects of aldosterone while limiting side effects associated with nonspecific steroid receptor binding. The compound is being developed for the treatment of hypertension

The NDA, for the indication of hypertension, was submitted on November 28, 2001 and the Acknowledgement Letter, dated December 17, 2001, indicating a Standard Review was issued to the sponsor. The sponsor requested this teleconference, with the Division, to discuss why they believe eplerenone meets the criteria for Priority Review. The sponsor faxed a copy of the briefing slides summarizing their position for Priority Review on January 11, 2002.

Discussion Points

Priority Review

The sponsor presented their position for Priority Review. They believe that Eplerenone addresses an unmet public health need in the following hypertensive subpopulations:

- Blacks
- Low renin HTN
- Systolic HTN.

They stated that eplerenone has the following beneficial actions:

1. Black Hypertensives
    - Equally effective in Caucasians and Blacks regardless of baseline renin levels
    - Renal protective as monotherapy with additive effect in combination with ACE (angiotensin converting enzyme) inhibitor; the data from one placebo controlled study, that compared eplerenone with Losartan, shows a robust regression in micro-albuminuria
    - Small increase in potassium may be of benefit in reducing cardio-vascular risk contrasts findings in African American Study in Kidney Disease (AASK) trial
    - Enhanced efficacy in Blacks and low renin HTN [contrasts ACE/ARBs (angiotensin receptor Blockers)]; effective in systolic HTN
    - Decreases certain treatment limiting adverse drug reactions
    - Augments the cardio-vascular protection afforded by ACE inhibitors
    - ACE/ARBs have labeling of decreased effectiveness in Blacks and low renin HTN; eplerenone does not have this deficiency

2. Systolic Hypertension
    - Similar to other comparators in lowering BP
    - Renal protective (vs. amlodipine)
    - Well tolerated; rare orthostatic hypotension, peripheral edema, cough
    - Small increase in potassium may be of benefit in reducing CV risk contrasts findings in the Systolic Hypertension in the Elderly Population (SHEP) trial.

Dr. Lipicky stated that the Division does not agree. Eplerenone, for the indication of HTN, does not meet the criteria for Priority Review for the following reasons:

1. Eplerenone is "another" anti-hypertensive drug
2. There is another marketed drug with the same mechanism of action as eplerenone and it has similar pharmacodynamic properties that the sponsor believes are important in treating the hypertensive subpopulations identified above
3. The mechanisms of action and proposed benefits might be true but the sponsor does not have the data to support the model driven assertions discussed above
4. The Division does not recognize micro-albuminuria as an acceptable surrogate marker.

Additionally, Dr. Lipicky stated that we know ACE inhibitors are not as effective in lowering blood pressure in Blacks; the finding that eplerenone was superior to an angiotensin receptor blocker is not startling. How eplerenone compares to diuretics and beta-blockers in the Black hypertensive population is not known.

The sponsor noted that there are other anti-hypertensive drugs that received Priority Review. Dr. Throckmorton explained that, in that instance, the sponsor had two, prospective designed trials comparing two drugs head to head to demonstrate efficacy in lowering blood pressure. Dr. Lipicky noted, in retrospect, that he believes the Priority Review determination was a bad judgement.

Dr. Lipicky suggested the sponsor might want to discuss their request for Priority Review with Dr. Temple.

(b)(5)

Carcinogenicity Issues

There was a discussion regarding the renal tumor findings in the 2-year chronic carcinogenicity study for the high dose female and placebo control male rat groups. It was concluded that the sponsor will evaluate the tissue slides for all dose groups (female and male) in both the 2-year chronic carcinogenicity ad lib and the 2-year chronic carcinogenicity diet controlled rat studies. The sponsor stated they did not need a written response from the Division indicating the required additional kidney tissue data.

The sponsor asked if the new carcinogenicity data would be presented to the Carcinogenicity Advisory Committee (CAC). Dr. Lipicky stated that the carcinogenicity data would be presented to the CAC after the Division completed their reviews. Additionally, if a priority Review is granted and the sponsor waits to submit the carcinogenicity data, the action date will be very close to the time the data are available for the CAC and approval is not likely. Dr. Lipicky stated that the Division needs the data 2-3 months ahead of the action date. The sponsor indicated that they are committed to the kidney tissue evaluation and will have the data submitted to the Division in less than six months.

Advisory Committee

The sponsor asked if eplerenone (for the indication for hypertension) would be presented to the Advisory Committee. Dr. Lipicky identified the following scenarios that could impact the decision to present at the Advisory Committee:

1. Dr. Temple agrees to grant Priority Review based on meeting the unmet need of a minority population would be presented to the Advisory Committee
2. A Priority Review and carcinogenicity is questionable, the drug approval is unlikely for the indication for hypertension and would be presented to the Advisory Committee
3. A Standard Review and carcinogenicity is questionable, for the indication for hypertension, would probably be presented to the Advisory Committee
4. A Standard Review and the carcinogenicity issues are resolved, for the indication for hypertension, would probably not go to the Advisory Committee
5. (b)(5)

Conclusions/ Recommendations

- The Division will schedule a teleconference between Dr. Temple and the sponsor to discuss their request for Priority Review.

- The sponsor will evaluate and submit the additional kidney tissue data for all dose groups (female and male) in both, the 2-year chronic carcinogenicity ad lib and the 2-year chronic carcinogenicity diet controlled rat studies.

Signature recorder: /S/ 1/29/02
Daryl Allis

Concurrence, Chair: /S/ 1/30/02
Raymond Lipicky, M.D.

Draft: 01/17/021 Final: 01/24/02
RD:
Throckmorton 01/23/02
Karkowsky 01/23/02
Marcinak 01/23/02
Morgenstern 01/24/02

Minutes of a Tele-conference

Date of Meeting: December 21, 2001

IND Number: [redacted] (Eplerenone)
Drug Class: Diuretic

Sponsor: G.D. Searle LLC

Meeting Chair: Albert DeFelice Ph.D.

Meeting Participants:

FDA

Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HDF-110
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
Daryl Allis, M.S.N., F.N.P.	Regulatory Health Project Manager, HFD-110

G.D. Searle LLC

Donald Raineri, Pharm.D.	Director, Global Regulatory Affairs

Background

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist (SARA). The compound is being developed for the treatment of hypertension [redacted]

The pre-clinical data submitted to the IND [redacted] for eplerenone revealed carcinogenicity concerns. The standard 2-year chronic toxicity/carcinogenicity rat study reported thyroid tumors that were expected. There was an increase in renal tumors in the female rat. The female rat metabolizes the drug (eplerenone) differently in that more drug is excreted unchanged in the urine of female rats and there is more nephropathy in female rats compared to male rats. Additionally, renal cell tumors were also found in two male rats in the placebo control group. There was a teleconference, between the Division and the sponsor on December 20, 2001, to discuss the carcinogenicity findings.

The purpose of this teleconference to provide the sponsor with Division's experience from other studies where there were carcinogenicity issues and serial sectioning of the tissues were required.

Meeting

Dr. DeFelice noted that the issue of serial sectioning and blind/coded reading of tissue samples has come up before. This request is not unique to this drug application. The Division leaves the sectioning and reading of the tissue slides up to the sponsor and their experts.

Dr. [redacted] referenced a paper that was published in 1994 in *Toxicologic Pathology* describing the process for histopathologic evaluation of multiple sections of kidney tissue. The sponsor is planning on following the guidelines discussed in this article. Additionally, Dr. [redacted] stated that

the database for the additional tissue sections would be kept separate from the original data; the new data will come from new slides. Dr. DeFelice agreed that the plan described by Dr. — was reasonable.

Dr. DeFelice stated that other sponsors have used pathologists from the National Toxicology Program (NTP) or the National Cancer Institute (NCI) to review tissue slides. Dr. — indicated that he did not think the sponsor wanted to utilize either of these resources. G.D. Searle LLC is planning to incorporate an internal peer review process — to assist in reading the slides as — participated in the evaluation of the original data.

There was a discussion focusing on what tissue slides would be included in the re-reading and additional serial sectioning for the original data submitted to the Division. Dr. DeFelice stated that in his opinion, the sponsor should include, at a minimum, the high dose and placebo control groups for both males and females. He explained that from a metabolic/toxicologic standpoint, there was two-times the body burden in females versus males. Therefore, tissue slides from both genders should be included in the follow-up evaluation and data from males and females could not be collapsed. Dr. — indicated that the sponsor would prepare and submit their rationale for only looking at the high dose and control groups in female rats.

Recommendations/Conclusions

The sponsor will follow the guidelines for evaluating multiple sections of kidney tissue as described in the literature referenced above. They will incorporate an internal peer review process for establishing reliability as well as using an outside consultant/expert in evaluating the tissue slides.

The sponsor will submit their rationale for only looking at the slides of the females in the high dose and control group within the next few weeks. They, however, will start the reexamination of the original tissue data for the females in the high dose and control group, as described above and discussed in the teleconference between the Division and the sponsor on December 20, 2001. The Division will notify the sponsor when a final decision has been reached regarding the study groups that need to be included in the follow-up evaluation.

/S/

Meeting Recorder: _____
Daryl Allis, M.S.N., F.N.P

/S/

Concurrence, Chair: _____
Albert DeFelice, Ph.D.

cc:
HFD-110/Mathews

Draft:	12/31/01	Final:	01/02/02
Hausner	01/02/02		
DeFelice	01/02/02		

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

Transmitted to FAX Number:	847-982-8152
Attention:	**Dr. Donald L. Raineri**
Company Name:	G.D. Searle LLC
Phone:	847-982-4751
Subject:	T-con Meeting Minutes, December 21, 2001
Date:	01/4/02
Pages including this sheet:	3

From:	**Daryl Allis**
Phone:	**301-594-5309**
Fax:	**301-594-5494**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

Please let me know you received this. Thank you.

cc:
Orig.
HFD-110
HFD-110/DAllis /Matthews

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
1/4/02 01:51:10 PM

Minutes of a Tele-conference

Date of Meeting: December 20, 2001

IND Number: [redacted] (Eplerenone)
Drug Class: Diuretic

Sponsor: G.D. Searle LLC

Meeting Chair: Douglas Throckmorton, M.D.

Meeting Participants:

FDA

Douglas Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HDF-110
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
Roswitha Kelly, M.S.	Statistician, HFD-710
Thomas Marciniak, M.D.	Medical Officer, HFD-110
Natalia A. Morgenstern	Chief, Project Management Staff, HFD-110
Daryl Allis, M.S.N., F.N.P.	Regulatory Health Project Manager, HFD-110

G.D. Searle LLC

Donald Raineri, Pharm.D.	Director, Global Regulatory Affairs
Winifred Begley	Senior Director, Global Regulatory Affairs
Susan Garthwaite, Ph.D.	Global Project Leader/Senior Director
Michael Schlosser, Ph.D.	Senior Director, Toxicology
Arthur Roth, Ph.D.	Fellow, Pre-clinical Statistics

Background

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist (SARA). The compound is being developed for the treatment of hypertension [redacted] The NDA (21-437) for eplerenone for the indication of hypertension (HTN) was submitted on November 28, 2001.

The pre-clinical data submitted to the IND [redacted] for eplerenone revealed carcinogenicity concerns. The 6-month Transgenic Mouse study did not have any carcinogenicity issues. The standard 2-year chronic toxicity/carcinogenicity rat study reported thyroid tumors that were expected. There was an increase in renal tumors in the female rat. The female rat metabolizes the drug (eplerenone) differently in that more drug is excreted unchanged in the urine of female rats and there is more nephropathy in female rats compared to male rats. Additionally, renal cell tumors were also found in two male rats in the placebo control group. The sponsor has additional data from a 2-year diet controlled carcinogenicity study in rats that have not been analyzed and evaluated.

The pharmacologist and statistician have been in contact with the sponsor regarding the rat carcinogenicity issues. Data tables and questions relating to the two-year rat chronic toxicity/carcinogenicity study were faxed to the sponsor on December 5, 2001 asking them to verify if they agreed with the Division's numbers and findings.

The purpose of this meeting is to discuss the concerns related to the rat carcinogenicity findings and provide the sponsor with the Division's recommendation for further action.

Meeting

Dr. Throckmorton noted that the Division had received the sponsor's response to the questions the Division faxed to them on December 3, 2001. The discussion today, however, would focus on what the Division believes are significant carcinogenicity concerns for eplerenone as it appears that eplerenone, pending additional data, causes renal neoplasia in female rats.

The sponsor stated that biological pattern does not fit carcinoma in the kidney. A true carcinoma response would show increased carcinomas as well as an increase in precursor cells, i.e., hyperplasia; this pattern is not there for eplerenone. Additionally, they noted that kidney carcinomas were found in two male rats in the control group.

Following a lengthy discussion, the Division and sponsor agreed that the carcinogenicity concerns need resolution. Dr. Throckmorton explained that Dr. Lipicky considered these unresolved concerns to be possible filing issues for the NDA. The Division, therefore, requests the sponsor to commit to the following plan:

- Re-read the pertinent slides from the standard 2-year chronic toxicity/carcinogenicity rat study in a blinded/coded fashion, to include both males and females.
- Conduct a serial sectioning and reading of the renal tissue from the standard 2-year chronic toxicity/carcinogenicity rat study in a blinded or coded fashion, to include both males and females.
- Complete the sectioning and blinded/coded histopathologic evaluation of the kidneys from the 2-year diet-controlled carcinogenicity study in rats.

The Division believes that examining additional sections throughout the kidney will provide a more thorough and representative characterization between drug exposure and changes in the kidney. The Division has experience with other drugs where additional tissue sections were requested. When the additional slides were evaluated in a blinded/coded fashion, tumors were found in other groups, i.e., control. The final tumor incidence analysis did not show a significant difference between the treatment and control groups.

The sponsor stated that they did not understand why they needed to re-read the slides and conduct the serial sectioning on the tissues already submitted since there are no indications of hyperplasia and this type of tumor is rare.

Dr. Throckmorton replied that this drug (eplerenone) is being developed for an indication that is required to be risk averse and we have findings that are not replicated in other drugs used for the same indication. We, therefore, have to take these concerns seriously and ask to see the pertinent data.

The sponsor noted that there is another drug [redacted] on the market for [redacted] Dr. Throckmorton explained that we are not talking

about [redacted] eplerenone is being developed for mild-to-moderate hypertension and there are already many other treatment options available.

The sponsor asked if they could re-read and conduct the serial sectioning evaluation of the high dose and placebo control groups for females only. Dr. Throckmorton stated that he needed to discuss this with Dr. Lipicky. He suggested that the sponsor send the Division their rationale for looking only at the females in the high dose and control group (for the data that has already been submitted) in addition to evaluating the 2-year diet controlled carcinogenicity study in male and female rats.

The sponsor asked if the new data will be submitted to the Carcinogenicity Advisory Committee (CAC) or will the data stay within the Division. Drs. Hausner and DeFelice explained that a carcinogenicity summary and the sponsor's tables and incidence findings were circulated to the CAC in July 2001 in addition to an oral presentation for the CAC. The CAC had questions and we have been back and forth with Drs. [redacted] and Raineri since that time discussing the carcinogenicity concerns. The newly generated data will be sent to the CAC.

The sponsor asked if the Division expected the new data to be available by the NDA filing date and if these data would impact the decision to give the application a standard or priority review. Dr. Throckmorton stated that the Division is asking for a commitment, from the sponsor, to provide the additional data; we do not expect the data to be available by the filing date. The additional carcinogenicity data will not impact the decision to assign a standard or priority review for the NDA. The possible issue for filing is whether or not we have adequate data to evaluate the application fully.

Recommendations/Conclusions

The Division requests that the sponsor commit to the following:

- A re-reading of the pertinent slides from the standard 2-year chronic toxicity/carcinogenicity rat study done in a blinded or coded fashion.
- Serial sectioning and evaluation of the renal tissue from the standard 2-year chronic toxicity/carcinogenicity rat study.
- Sectioning and blinded/coded histopathologic evaluation of the kidneys from the 2-year diet-controlled carcinogenicity study in rats.

The sponsor will submit their rationale for looking only at the female high dose and placebo control groups in addition to submitting the data for the 2-year diet controlled carcinogenicity rat study in both sexes within the next few weeks.

Drs. Hausner and DeFelice will have a teleconference with Drs. [redacted] and Raineri to discuss the Divisions experience with other studies where there were carcinogenicity issues and serial sectioning of the tissues were required.

Dr. Throckmorton will discuss the sponsor's request to look at the high dose and control group for females only with Dr. Lipicky. The Division will inform the sponsor when a decision is made.

Meeting Recorder: S 1-4-02
Darvl Allis

Concurrence, Chair: S 1.4.02
Douglas Throckmorton, M.D.

cc:
HFD-110/Mathews

Draft:	12/27/01	Final:	01/04/02
Hausner	01/02/02		
DeFelice	01/02/02		
Keily *			
Marciniak	01/02/02		
Throckmorton	01/02/01		
Morgenstern	01/03/02		

* Draft sent electronically

Minutes of Internal Meeting

Date of Meeting: December 3, 2001

IND Number: [redacted] (Eplerenone)
Drug Class: Diuretic

Meeting Chair: Raymond Lipicky, M.D.

Meeting Participants:

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HDF-110
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
Daryl Allis, M.S.N., F.N.P.	Regulatory Health Project Manager, HFD-110

Background

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist (SARA). It is a steroid nucleus-based antimineralcorticoid 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 compound is being developed for the treatment of hypertension [redacted] The initial NDA submission will include efficacy and safety data to support the use of eplerenone for the treatment of hypertension (HTN).

Previous correspondence and meetings between the Division and the Sponsor include:

1. Pre-IND meeting, January 17, 1996
2. IND [redacted] submitted on October 24, 1996
3. FDA CAC approval of the alternate mouse model for carcinogenesis assessment (p53 knockout mouse model) in November 1997, and dosage selection for the rat and mouse carcinogenesis studies in December 1996 and November 1998, respectively.
4. EOP2 meeting for HTN on July 17, 1998

6. Pre-NDA meeting, July 19, 2001
7. Pre-NDA CMC meeting, July 31, 2001.

Dr. Hausner has submitted a summary of primary rodent carcinogenicity findings.
Ms. Roswitha Kelly has submitted a statistical review and evaluation of the Two-Year Carcinogenicity Study in Rats and 26-Week Study in p53 Transgenic Mice. The purpose of this internal meeting is to discuss the rat carcinogenicity findings.

Meeting

Dr Hausner stated that the 6-month Transgenic Mouse study did not have any carcinogenicity issues. The two-year rat study reported thyroid tumors that were expected. An unexpected finding, however, was an increase in renal tumors in the female rat. The female rat metabolizes the drug (Eplerenone) differently in that more drug is excreted unchanged in the urine of female rats and there is more nephropathy in female rats compared to male rats.

The statistical review submitted by Ms. Kelly was discussed. She indicated that the sponsor employed some non-standard statistical methods for testing and she summarized the following concerns:

- The sponsor used individual days as time intervals.
- The sponsor used alpha levels relevant to two-year carcinogenicity studies not to one whole-life and one short-term study.
- The statistical reviewer could not reconcile differences in the numbers of animals surviving till terminal sacrifice between various sponsor reports and tabulations from the electronic data set.
- The sponsor did not consider the increase in mortality with dose statistically significant for the female rats.
- In addition to the statistically significant findings in thyroid adenomas (both sexes) and combined adenomas and carcinomas (females only) which the sponsor mentioned, the statistical reviewer found follicular cell carcinoma of the kidney and follicular cell adenoma and carcinoma combined statistically significant among the female rats.

Recommendations

Dr. Lipicky recommended that the Division discuss the findings of the statistical review with the sponsor to verify if they agree with the numbers and the Division's findings.

Additionally, request that the sponsor provide the following:

- A re-reading of the pertinent slides from the standard 2-year chronic toxicity/carcinogenicity rat study done in a blinded or coded fashion.
- Serial step sectioning and reading of the renal tissue from the standard 2-year chronic toxicity/carcinogenicity rat study in a blinded or coded fashion.
- Sectioning and blinded/coded histopathologic evaluation of the kidneys from the 2-year diet-controlled rat study.

Meeting Recorder: S 1-4-02

Concurrence, Chair: S ✓

cc:
HFD-110/Mathews

Draft:	12/13/01	Final:	12/26/01
Hausner	12/17/01		
DeFelice	12/20/01		
Pelayo	12/20/01		
Stockbridge	12/20/01		
Throckmorton	12/21/01		

Pre-NDA CMC Meeting Minutes

Meeting Date: July 31, 2001

Type of Meeting: Pre-NDA CMC Meeting

IND Application: [redacted] Eplerenone (SC-66110)

Sponsor: G.D. Searle & Co.
Classification: B

Meeting Request Date: June 4, 2001
Confirmation Date: June 14, 2001
Briefing Package Received: July 5, 2001

Meeting Chair: Dr. Simmons
Meeting Recorder: Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

John Simmons, Ph.D.	Director, Division New Chemistry I
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Florian Zielinski, Ph.D.	Chemist, HFD-810
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 & Co.

Robert Baum, Ph.D.	Senior Director, Analytical Sciences
Stan Penzotti, Ph.D.	Executive Director, Pharmaceutical and Analytical Sciences
Brian Whelihan	Section Head, Analytical Sciences
Jennifer Stanek	Director, CMC Regulatory Affairs

BACKGROUND

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist (SARA). It is a steroid nucleus-based antimineralcorticoid that effectively blocks aldosterone at receptor sites in tissues throughout the body, thereby antagonizing the pathological effects of aldosterone while limiting side effects associated with nonspecific steroid receptor binding. The compound is being developed for the treatment of hypertension [redacted] The initial NDA submission, which is planned for November 2001, will include efficacy and safety data to support the use of eplerenone for the treatment of hypertension (HTN). [redacted]

An End of Phase 2 Chemistry, Manufacturing and Control (CMC) meeting between the sponsor and the Division occurred on April 12, 1999.

The sponsor requested this meeting to discuss the CMC issues related to the pending NDA submission. They plan on requesting a priority review for this application. In addition, a Pre-NDA meeting was held with the Division on July 19, 2001, to discuss the format and content of the electronic NDA submission.

DISCUSSION

Dissolution

There was a discussion regarding dissolution versus disintegration tests. The sponsor noted that the dissolution and disintegration data appear to be correlated. The Division stated that they have not accepted disintegration data to date and our preference is dissolution tests. Dr. Marroum stated that the data submitted were acceptable. If disintegration data are submitted, the sponsor must demonstrate that the disintegration test is able to reject lots that are not acceptable from a bioavailability point of view. The sponsor stated that they are planning on submitting dissolution data in the NDA.

Tablet Shape/ Particle Size

The sponsor noted the dissolution and disintegration tests used — tablets and the commercial tablets will be — The particle size will remain the same for both tablets. The sponsor wanted to know if this would present a problem. The Division informed the sponsor that this should not be a problem if they can show that the dissolution profiles are comparable.

The sponsor noted that — sample tablets may be submitted instead of the — but the data regarding the drug substance, dissolution and bioequivalence would not change. The Division stated that this would not be a problem.

Starting Material

Drug Substance

The sponsor noted that dog studies were in process to assure the expected bioavailability of the drug.

The Division asked if [redacted] was used to identify the polymorphs. The sponsor confirmed that [redacted] was used.

Drug Substance Specifications

The Division could not comment on the proposed limits because this is a review issue. Generally, limits should be based on batch data taking into account manufacturing and analytical capability. This is also true for residual solvents where limits should not be set at the maximum levels allowed by ICH Q3C. The single point particle size specification was discussed, and the Division asked the sponsor to justify the adequacy of this in the NDA.

Drug Product Specification

There are no concerns regarding the drug product specifications. The sponsor was asked why there were no specifications for moisture content. The sponsor responded that no limits were needed since there was no significant increase on storage.

Registration Stability

There are no concerns with registration stability. There are no changes in the data previously submitted.

Batch Records

The sponsor's proposal was acceptable to the Division.

Administrative Issues

The formatting of the application, standard NDA versus Common Technical Document (CTD), was discussed and the Division indicated that for the CMC section, the standard NDA format is preferred. The sponsor and the Division agreed upon submitting an electronic application following the conventional format with paper copies of select sections of the application, as requested by the Division. The Division recommends following the Good Practice Standards and the Guidance for Industry: Providing Regulatory Submissions in Electronic Format- NDAs, dated January 1999.

The issue of accessing the electronic data in the field was discussed. The sponsor agreed to supply a paper copy or a CD-ROM for the field copy.

Conclusion

There were no major issues identified. The sponsor agreed to complete the dissolution tests and characterize the bioavailability of the drug product. The drug specifications described in the briefing documents are acceptable with the Division.

Signature recorder: /S/

Concurrence, Chair: /S/

Draft:	08/09/01	Final:	08/30/01
RD:			
Simmons	08/30/01		
Srinivasachar	08/16/01		
Zielinski	08/16/01		
Marroum	08/16/01		
McDonald	08/30/01		

cc:
Orig.
HFD-110
HFD-110/DAllis /Matthews

Pre-NDA Meeting Minutes

Meeting Date:	July 19, 2001
Type of Meeting:	Pre-NDA Meeting
IND Application:	[redacted]Eplerenone (SC-66110)
Sponsor:	G.D. Searle & Co.
Classification:	B
Meeting Request Date:	June 6, 2001
Confirmation Date:	June 18, 2001
Briefing Package Received:	June 28, 2001
Meeting Chair:	Douglas Throckmorton, M.D.
Meeting Recorder:	Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Biopharmaceutics, HFD-860
Jorge Rios, M.D.	DSI Liaison, HFD-110
Natalia A. Morgenstern	Chief, Project Management Staff, HFD-110
Daryl Allis	Regulatory Health Project Manager, HFD-110

G.D. Searle & Co.

Richard Bittman, Ph.D.	Director, Cardiovascular & Non-Clinical Statistics, Statistics and Programming
Elizabeth Canning	Executive Director, Cardiovascular Products
Susan Garthwaite, Ph.D.	Global Project Leader/Senior Director, Global Project Development
Jay Kleiman, M.D., M.P.A.	Medical Director, Cardiovascular and Metabolic Diseases Clinical Research
Ellen McMahon, Ph.D.	Director, Cardiovascular and Metabolic Diseases Discovery Research
Mark Milton, Ph.D.	Assistant Director, Global Drug Metabolism
Donald Raineri, Pharm.D.	Director, Global Regulatory Affairs
Barbara Roniker, M.D.	Senior Director, Cardiovascular and Metabolic Diseases Clinical Research
Michael Schlosser, Ph.D.	Senior Director, Global Toxicology
Myrlene Staten, M.D.	Vice President, Cardiovascular and Metabolic Diseases Clinical Research
Dwain Tolbert, Ph.D.	Program Leader, Clinical Pharmacology

Background

Eplerenone (SC-66110) is a highly selective aldosterone receptor antagonist (SARA). It is a steroid nucleus-based antimineralcorticoid that effectively blocks aldosterone at receptor sites in tissues throughout the body, thereby antagonizing the pathological effects of aldosterone while limiting side effects associated with nonspecific steroid receptor binding. The compound is being developed for the treatment of hypertension.

The initial NDA submission, which is planned for November 2001, will include efficacy and safety data to support the use of eplerenone for the treatment of hypertension (HTN).

Previous correspondence and meetings with the Division include:

1. Pre-IND meeting, January 17, 1996
2. IND — submitted on October 24, 1996
3. EOP2 meeting for HTN on July 17, 1998

5. FDA CAC approval of the alternate mouse model for carcinogenesis assessment (p53 knockout mouse model) in November 1997, and dosage selection for the rat and mouse carcinogenesis studies in December 1996 and November 1998, respectively.

The sponsor requested this meeting to discuss the format and content for an electronic NDA submission. They plan on requesting a priority review and a deferral of the requirement to submit studies with eplerenone in pediatric patients until after the NDA is approved. In addition, a Pre-NDA CMC meeting is scheduled with the Division on July 31, 2001.

Meeting

The sponsor requested clarification and/or confirmation from the Division on the following issues and questions:

Preclinical Pharmacology

Consistent with the ICH S3A Guideline on Toxicokinetics, in non-clinical toxicology studies we propose to express plasma exposure exaggerations based on non-protein bound eplerenone (the active, ring-closed form). Does the Agency agree?

- The Division agreed, providing there are protein bound data.

Integrated Summary of Efficacy (ISE)

1. Is the general organizational plan and proposed content of the ISE document satisfactory?

   - The organizational plan and proposed content of the ISE document is acceptable with the Division.

2. Intent-to treat (ITT) cohort (Primary analysis)

   Our primary blood pressure efficacy endpoint is the change from baseline to last BP observation obtained before the patient's last dose of study medication, plus one day. Therefore, we define the ITT cohort to be all randomized patients with a base line BP measurement and at least one post-randomization BP measurement obtained before last dose of study medication, plus one day. Does the Agency agree with this approach?

   - The Division agreed.

3. Evaluable cohort (for non-inferiority trials; secondary analysis)

For non-inferiority trials, ICH guidelines recommend performing an evaluable ("per protocol") analysis, in addition to the ITT analysis. We propose to define this cohort to consist of all ITT patients who met key inclusion and exclusion criteria, who took study drug for at least 28 days, and who did not take certain excluded medications at any time during the trial (e.g., reserpine or guanethidine). Given this cohort, the LOCF (last observation carried forward) analysis will analyze change from baseline to the last visit at which the patient was at least 80% compliant with taking study medication since the previous visit, took study medication one day before the visit and did not take certain excluded medications (e.g., non-protocol antihypertensives, systemic glucococorticoids) within 2 days before the visit. Does the Agency concur with this approach?

- The Division will review the data. However, with respect to non-inferiority trials, the Division ordinarily does not pay great attention to these data. These data usually do not impact the approval or non-approval process, absent a find of superiority or inferiority.

4. Dose-response

The dose-response of eplerenone will be characterized by pooling the results of the two fixed-dose, placebo-controlled ABPM and cuff studies (-010, -049). The primary efficacy measure will be change from baseline in seated trough cuff DBP. Secondarily, dose-response will be assessed for change from baseline in seated trough cuff SBP, and for ABPM summaries, such as change from baseline in 24-hour DBP and SBP. As a supplemental analysis, we will also explore dose-response from the titration-to-effect studies (-016, -018, -019, -020, -022, -023, -024, -026). Does the Agency concur with this approach to establish the dose-response?

- The Division agreed.

5. Subgroups

We plan to analyze data across studies in the following subgroups: age (elderly defined as >=65, also as >=75), weight, race, gender, diabetic status, patients with baseline systolic hypertension (SBP ≥150 mm Hg and <165 mm Hg, and PP≥ 70 mm Hg; or SBP≥ 165mm Hg and < 200 mm Hg, and DBP < 95 mm Hg), patients with elevated urinary albumin to creatinine ratio (UACR) (>=30 mg/g, also >= 100 mg/g), and patients with elevated baseline collagen markers (to be determined). The main purpose of the analyses based on age, weight, race, gender and diabetic status is to assess differential effects of eplerenone. The main purpose of the analysis based on elevated SBP, elevated UACR and elevated collagen markers is to assess efficacy (change from baseline in SBP, UACR and collagen markers, respectively) in these populations. Does the Agency concur with this choice of subgroups?

- The Division agreed.

6. Data Sets

SAS data and programs will be provided only for the primary efficacy analyses. Does the Agency agree?

- The Division needs to see all the data, including safety data. The statisticians need to see the programs for the codes to complete the analyses and the medical reviewers need to see the programs that establish the primary efficacy analysis.

Integrated Summary of Safety (ISS)

1. Is the general organizational plan and proposed content of the ISS acceptable?

   - The general organizational plan and proposed content of the ISS is acceptable to the Division.

2. In addition to standard safety analyses, the following have been identified as safety events of interest for this agent:
   a. Hypotension reported as an adverse event (AE)
   b. Potassium: AE or laboratory criteria
   c. Renal: AE or laboratory criteria
   d. Uric acid: AE or laboratory criteria
   e. Liver function tests: AE or laboratory criteria
   f. Impotence
   g. Gynecomastia
   h. Menstrual irregularities.

   Does the Agency agree with our plans for considering these safety events of primary interest for eplerenone?

   - The Division agreed. The sponsor will report all adverse events regardless of causality.

3. Based on prior experience with spironolactone, the eplerenone toxicity study results, and the mechanism of action, which is not known to affect cardiac repolarization, we do not anticipate QT prolongation due to eplerenone. QT interval assessment will, however, be performed with ECG's obtained at the specified timepoints.

   Does the Agency agree with our plan to evaluate the effect (if any) of eplerenone on QT interval duration?

   - The Division agreed with the plan and will review the data.

4. We will provide sub-group analyses of renal, hepatic or lipid alterations based on prospectively defined baseline laboratory cut-off results (rather than baseline medical histories derived from CRF's). Does the Agency agree with our plan?

   - The Division agreed.

Organization of NDA

1. Does the Agency have any specific preferences or suggested modifications for the proposed content or structure?

   - The proposed content and structure of the NDA is acceptable with the Division.

2. We propose to submit an electronic submission and paper review copies the Application Summary Table of Contents. Is this acceptable to the Agency?

   - An electronic submission of the NDA is acceptable to the Division. There was a discussion regarding paper submissions of the complete archival volume and review copies. The sponsor stated they would submit paper copies of portions of the NDA, if requested by the Division. The Division request for paper copies would be communicated to the sponsor at a later date.

- Addendum to the minutes: The Division requests seven (7) paper copies of Volume 1.1, cover letter and FDA Form 356h (archival copy, desk copy and a copy for each reviewer).

Labeling

We plan to seek label indication for eplerenone as monotherapy or in combination with other antihypertensive therapies for the treatment of hypertension and recommend once daily dosing starting at 50 mg/day up to 200mg/day. Does the Agency concur with our proposed statements?

- The content of the labeling, with respect to indications and dose administration, will be data driven. Therefore, the Division can not comment on the above statements at this time.

Pediatric Use

We plan to seek a deferral [as described in CFR 314.55(b)] of the requirement to submit studies with eplerenone in pediatric patients [described in CFR 314.55(a)] until after the NDA is approved on the basis that the product will be ready for adult use before pediatric data will be available. The NDA for hypertension will include a Pediatric Use section, as required by CFR 314.50(d)(7), with certification of the grounds for deferral,

Does the Agency agree with this plan?

- The Division agreed to grant a deferral of the requirement to submit studies with eplerenone in pediatric patients in the initial NDA application.

Priority Review

Based on the FDA Priority Review Policy (MAPP 6020.3, dated April 22, 1996), we plan to seek a Priority Review of our NDA on the basis that eplerenone, if approved, would provide a significant improvement compared to marketed products for the treatment of hypertension in certain subgroups of patients. Improvement will be demonstrated by evidence of increased effectiveness in black patients, patients with systolic hypertension, and in diabetic patients with hypertension. Blood pressure lowering will be complemented by the evidence of long-term protection of target organs – renal protection (reduced microalbuminuria) in hypertensive diabetics and in blacks, and enhanced vascular compliance in patients with systolic hypertension. Further, based on direct comparisons, the tolerability profile of eplerenone is similar to the [redacted] agent on the market, [redacted] and superior to that of spironolactone, the only other agent with the same mechanism of action.

- The Division needs to see the data from the studies. Dr Temple will make the decision to grant a Priority Review. Therefore, we can not comment on this request at this time.

- The results of the studies need to demonstrate an effect on clinical outcomes in order to consider granting a Priority Review (e.g. demonstrate a sustained effect on microalbuminuria off drug; link the effect of the drug to change in renal morbidity; affect the natural history of diabetic nephropathy). The Division has not accepted microalbuminuria as a surrogate marker of clinical benefit; we know drugs that lower blood pressure lower microalbuminuria. We do not have data to support this as a primary end-point.

1.

(b)(5)

Signature recorder: /S/ 8/10/01

Concurrence, Chair: /S/

Draft:	07/26/01	Final:	08/08/01
RD:			
Throckmorton	07/27/01		
Stockbridge	07/27/01		
Pelayo	07/27/01		
Hausner	07/27/01		
Marroum	07/27/01		
Rios			
Morgenstern	08/03/01		

MEETING MINUTES

APR 26 1999

Date: April 12, 1999

Subj: IND [redacted] Eplerenone
End of Phase 2 Meeting-CMC

Sponsor: Searle
4901 Skokie Parkway
Skokie, IL 60077

Meeting Chair: Charles Hoiberg, Ph.D.
Recorder: Gary Buehler
Sponsor Lead: Various

Attending:

Searle	
Dr. Arthur Campbell	VP, Product Development
Dr. Robert Baum	Senior Director, Analytical Development
Dr. Sean Nugent	Senior Director, Chemical Sciences
Dr. Stan Penzotti	Executive Director, Pharm. and Analytical Sciences
Brian Whelihan	Section Head, Analytical Development
Jennifer Stanek	Manager, Regulatory Affairs
FDA	
Charles Hoiberg, Ph.D.	Director, Division of Chemistry I, HFD-810
Kasturi Srinivasachar, Ph.D.	Team Leader, Cardio-Renal Division, HFD-810
Patrick Marroum, Ph.D.	Team Leader, Division of Pharm. Evaluation I, HFD-860
Gabriel Robbie, Ph.D.	Clinical Pharmacology Reviewer, HFD-860
Florian Zielinski, Ph.D.	Chemistry Reviewer, HFD-810
Gary Buehler	Project Manager, HFD-110

BACKGROUND

Eplerenone (SC-66110) is being developed for the treatment of hypertension
It is a steroid-based antimineralocorticoid that acts as a competitive inhibitor of aldosterone at aldosterone receptor sites in various tissues throughout the body. An NDA submission for this product is expected in the first or second quarter of 2001.

DISCUSSION

Dissolution

The firm was given the following recommendations for developing their dissolution specification:

1. Include the rationale for the selection of the dissolution specification in their NDA. Include the data for the usual media for later reference as well as data used to optimize their specification.
2. Justify the choice of rotation speed.
3. Justify the choice of SDS concentration.
4. Aim to set the specification so that it passes at Specifications that are set to always pass at are usually too lenient and are, therefore, not discriminating.
5. Preliminary dissolution data may be submitted to the IND for review as soon as they are ready.

Tablet Shape

The firm was informed that comparative dissolution testing would be adequate to qualify a different tablet shape.

Particle Size

The firm stated that they intend to set the particle size specifications based on material used in the clinical trials and processing studies. From preliminary data, it appears that the bioavailability is not affected by the particle size.

Starting Material

FDA considers SC-66107 a pseudo-starting material. As such, FDA requires the following safeguards, since the manufacture of this substance is not subject to CGMP inspection:

1. Searle should submit a flow diagram of the syntheses to the IND (not more than about 10 pages total) for review prior to the NDA submission.
2. Searle should include the syntheses of the starting material for each supplier in the NDA submission.
3. Searle should contact FDA regarding the reporting requirements, if a new supplier of starting material is requested. The reporting requirements depend on the degree of change requested.

Starting Material SC-66107

Purification

Searle will provide data to show that all impurities are more soluble in methyl ethyl ketone than in ethanol. If they are not, they will have an in-process specification for residual in the crude concentrate before ethanol digestion.

Polymorphs

Searle will develop specifications for polymorphs for the drug substance. They will control to % or less for polymorph I and will monitor interconversion between I and II during their stability program.

Searle will demonstrate that the presence of polymorph I does not affect the therapeutic index of the product.

Stability Protocol

The firm was informed that their proposed stability protocol was acceptable.

Identity Test for Active in Drug Product

The specification proposed retention time and optical rotation to identify the active. This combination does not fit the strict definition of an identity test. The firm will determine if these two tests

discriminate between their currently manufactured products. Dr. Zielinski will contact Steve Miller for additional guidance.

ACTION ITEMS

1. Searle will determine if the combination of retention time plus optical rotation is adequate to discriminate between their currently manufactured products.
2. Dr. Zielinski will contact Dr. Steve Miller (or Eric Sheinin) to establish identity test requirements and then inform Jennifer Stanek at Searle of the outcome of the discussion.

Minutes taken by: /S/ 4/26/99
Gary Buehler

Concurrence, Chair: /S/ 4/29/99
Charles Hoiberg, Ph.D

Orig IND
HFD-110
HFD-110 GBuehler
HFD-110 SBenton

RD:	FZielinski	4/12/99
	KSrinivasachar	4/12/99
	GRobbie	4/13/99
	PMarroum	4/13/99
	CHoiberg	4/24/99

AUG 5 1998

MEETING MINUTES

Date: July 17, 1998

Subj: IND — End of Phase 2 Meeting - Eplerenone for hypertension

Sponsor: Searle
4901 Searle Parkway
Skokie, IL 60077

Meeting Chair: Raymond Lipicky, M.D.
Recorder: Gary Buehler
Sponsor Lead: John Alexander, M.D.
Barbara Roniker, M.D.

Attending:

Searle

John Alexander, M.D.	Exec. VP, Clinical Research
Susan Garthwaite, Ph.D.	Sr. Project Manager, Project Management
ingrid Hoos	Manager, Regulatory Affairs
Barbara Roniker, M.D.	Director, Clinical Research
Donald Raineri, Pharm.D.	Director, Regulatory Affairs
Dwain Tolbert, Ph.D.	Assist. Dir., Clinical Research

FDA

Rachel Behrman, M.D.	Dep. Dir., ODE I, HFD-101
Raymond Lipicky, M.D.	Dir., Div. of Cardio-Renal Drug Prod., HFD-110
A. Karkowsky, M.D., Ph.D.	Medical Team Leader, HFD-110
Juan Carlos Pelayo, M.D.	Medical Reviewer, HFD-110
Lu Cui, Ph.D.	Biometrics Reviewer, HFD-710
Ahmed El-Tahtawy, Ph.D.	Biopharmaceutics Reviewer, HFD-860
Gary Buehler	Project Manager, HFD-110

Pre-Meeting Only

Robert Temple, M.D.	Director, ODE I, HFD-101
James Hung, Ph.D.	Acting Team Leader, Div. of Biometrics, HFD-710

BACKGROUND

Eplerenone is a highly selective aldosterone receptor antagonist (SARA). It is a steroid nucleus-based antimineralcorticoid which effectively blocks aldosterone at receptor sites in tissues throughout the body (i.e., heart, brain, vasculature). Clinical and preclinical studies have linked aldosterone to high blood pressure, cardiac hypertrophy, cardiac and vascular fibrosis, ventricular arrhythmias and increased mortality of patients with heart failure. Searle met with Dr. Lipicky — on May 29, 1998 to discuss their program for hypertension. At that meeting the discussion focused on using their Phase 2 dose ranging study and their planned Phase 3 factorial study as their major trials. They have also proposed a number of studies to evaluate eplerenone's effect on special populations and in combination with

other antihypertensives. They have requested this meeting to discuss their program with the Division and Dr. Temple.

DISCUSSION

General Program

The firm was informed that their proposal for the factorial trial, provided that additional cells were added to incorporate a wider dose range for HCTZ and higher doses of eplerenone, was acceptable. They were also informed that their proposed factorial trial combined with their dose-ranging trial (in addition to the requisite pharmacokinetic and interaction studies) would probably constitute an acceptable package to get a standard antihypertensive claim for eplerenone. The additional studies proposed to study eplerenone in special populations or comparing it to other antihypertensives were all considered less than useful, due primarily to the lack of a placebo group. It would not be possible to quantitate the effect of eplerenone when comparing it to other antihypertensives without a placebo group. The firm was also advised that, in order to claim any superiority in advertising or labeling to any established therapy, they would need two positive trials done comparing maximum doses of each drug. The firm was also advised that, when comparing their drug to an angiotensin receptor antagonist, was not the ideal choice because of its less than ideal characterization of upper dose.

The firm said that some of their trials were included because of requirements for registration in other countries. It was also mentioned that these studies were being proposed to try to differentiate their drug from other antihypertensives by emphasizing that inhibiting aldosterone will result in various positive effects. They were advised that they would not be permitted implicit labeling claims for effects that were not demonstrated in adequate and well-controlled trials.

Systolic Hypertension

The firm was advised that, in order to get a systolic hypertension indication, they would have to do a trial in a population that was similar to that used in the SHEP trial. This trial would also have to be of similar design to the SHEP trial (add on therapy) and the results be replicated in a second trial. The firm confirmed that if their drug was particularly effective for systolic hypertension in their factorial trial, this result in the subset could be used as the supporting (second) trial

Study in Blacks

The firm was informed that, in order to make a definitive statement with regard to efficacy in the black population, they would have to have a compelling package. The fact that blacks are included in the dose response and factorial trial will allow them to be included in the general hypertension indication. In order to make a superiority statement, however, they would need a placebo-controlled, dose-ranging trial that ideally would randomize both whites and blacks. This trial would have to show enhanced efficacy in the black population and be replicated before any statement relating to enhanced efficacy in the black population would be considered.

Metabolism Studies

Because eplerenone induces P450/3A4, the drug interaction profile must be worked up thoroughly. They will probably be asked to perform certain clinical drug interactions studies to determine which drugs can be safely taken with eplerenone and which drugs cannot. They were also advised to investigate the apparent non-linearity at higher doses. The firm said that they plan to do studies to define the kinetics of the drug. Indirect PK/PD analysis may answer some questions relating to high concentration, non-linearity adverse effects.

In addition, because the half-life of the drug does not support a once daily dosing regimen, they would probably have to confirm the finding in their dose-ranging trial that there is no difference in efficacy when the same daily dose of the drug is given once daily or twice daily. If this is not confirmed, the approved dosing regimen for the product will be "once or twice daily."

Factorial Trial

(b)(5)

Regarding their proposed trial with hydrochlorothiazide (HCTZ), they were advised to widen the range of HCTZ being studied (from 12.5-25 to 6 - 50 mg) and were also asked why they were not increasing the dose of eplerenone being studied. The firm presented data to show that single doses of eplerenone greater than 200 mg caused a high incidence of hyperkalemia; they therefore did not want to exceed that dose in their combination trials.

The firm was advised to use calculated/estimated creatinine clearance (from Cockroft-Gault Formula) instead of serum creatinine as the criterion for exclusion from the trial. They were also advised to do peak/trough ratios if they do not plan to use APBM in the trial.

EVENTUAL DEVELOPMENT STRATEGY

The firm said that they believe that eplerenone

product to decrease the hyperkalemia problem.

Minutes taken by: /S/ 7/23/98

Gary Buehler

Concurrence, Chair /S/ 9/12/98

Raymond Lipicky, M.D.

Orig IND
HFD-110
HFD-110 GBuehler
HFD-110 SBenton
HFD-101 RBehrman
HFD-101 RTemple

RD:	JPelayo	7/20/98
	AKarkowsky	7/25/98
	LCui	7/21/98
	AEl-Tahtawy	7/21/98
	RBehrman	7/27/98

Allis, Daryl

m: Allis, Daryl
nt: Thursday, September 12, 2002 2:35 PM
To: 'donald.l.raineri@pharmacia.com'
Subject: Inspra carton and container comments

Don,

I apologize for the delay. The medical reviewer needs another 30-60 minutes to add Dr. Throckmorton's latest comments.

I wanted to have this out no later than 1:00 pm. Best of plans.....

Attached are the carton/container comments.

Daryl

DMETS carton
ıtainer commen

In the review of the container labels and carton labeling of Inspra, DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

The firm has submitted a package size (30's) considered to be a "unit of use" package. Please verify that the sponsor intends to market with a child-resistant closure.

B. CONTAINER LABEL (Unit Dose)

1. Increase the prominence of the established name to be at least half the size of the proprietary name.

2. We encourage the use of boxing, colors or some other means to differentiate the strengths appearing on unit dose labels. If colors are used, please use the same colors used to differentiate strengths on container labels.

C. CONTAINER LABEL (100 mg)

The yellow color used to differentiate the strength of the 100 mg container label does not afford sufficient background contrast to ensure adequate prominence. We encourage the use of a color that will improve the readability of this labeling statement.

D. CARTON LABELING (Unit Dose 100's)

Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be in a child resistant container. We offer the following as an example:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used. [NOTE: The second sentence is optional]