CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-437

Correspondence

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 Raineri**
Company Name:	G.D. SearleLLC
Phone:	847-982-4751
Subject:	Inspra: Approval Letter with corrected labeling
Date:	10/8/02
Pages including this sheet:	22

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

PLEASE LET ME KNOW YOU RECEIVED THIS.

Daryl

MODE = MEMORY TRANSMISSION START=OCT-08 13:48 END=OCT-08 13:54

FILE NO.=163

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	s	918479828152	022/022	00:05:26

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

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 Rainerl**
Company Name:	G.D. SearleLLC
Phone:	847-982-4751
Subject:	Inspra: Approval Letter with corrected labeling
Date:	10/8/02
Pages including this sheet:	22

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

PLEASE LET ME KNOW YOU RECEIVED THIS.

Daryl

MODE = MEMORY TRANSMISSION START=SEP-27 16:53 END=SEP-27 16:57

FILE NO.=059

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	918475815179	022/022	00:04:04

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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

Transmitted to FAX Number:	847-581-5179
Attention:	**Dr. Donald Raineri**
Company Name:	G.D. Searle LLC
Phone:	847-982-4751
Subject:	Inspra: Approval Letter
Date:	9/27/02
Pages including this sheet:	21

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

Please call me to confirm that you received the letter.

It has been a pleasure to work you and your team.

Daryl

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-437

G.D. Searle LLC
Attention: Donald L. Raineri. Pharm. D.
4901 Searle Parkway
Skokie, IL 60077

Dear Dr. Raineri:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SC-66110 (Eplerenone) Tablets. Our December 17, 2001 letter referred to incorrect application and receipt dates. The correct dates are:

Date of Application: November 28, 2001

Date of Receipt: November 29, 2001

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 28, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 29, 2002.

We apologize for any inconvenience this may have caused you.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
301-594-5309

Sincerely,

{See appended electronic signature page}

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Natalia Morgenstern
1/4/02 04:40:14 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-437

G.D. Searle LLC
Attention: Donald L. Raineri, Pharm.D
4901 Searle Parkway
Skokie, IL 60077

Dear Dr. Raineri:

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

Name of Drug Product: SC-66110 (Eplerenone) Tablets

Review Priority Classification: Standard (S)

Date of Application: November 29, 2001

Date of Receipt: November 30, 2001

Our Reference Number: NDA 21-437

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 28, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 29, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Natalia Morgenstern
12/17/01 04:31:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 29 2002

Dear Dr. [redacted]

Between March 20 and 26, 2002, Ms. Sharon Matson, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol [redacted] of the investigational drug [redacted] (eplerenone), performed for Searle/Pharmacia. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we find that, except for the inadequate identification of the person who recorded the source data, you were in basic compliance with pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Matson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

[S]

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN:
Field Classification: VAI
Headquarters Classification:
_____1)NAI
___X_2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
____inadequate informed consent
____inadequate drug accountability
____failure to adhere to protocol
__X_inadequate records
____failure to report ADRS
____other
Deficiency Code: 6

cc:
HFA-224
HFD-110 Doc.Rm. NDA#21-437
HFD-110 Review Div.Dir. Throckmorton
HFD-110 MO (Marciniak)
HFD-110 PM (Allis)
HFD-46/47 c/r/s/ GCP File #10606
HFD-47 RS/KS
HFR-CE-850 DIB (Bigham)
HFR- CE-850 Bimo / Field Investigator (Matson)

r/d:**(RBS4/25/02)**
reviewed:AEH:**(4/25/02)**
f/t:mb:**(4/25/02)**
o:\RS\NDA21-437\.

Reviewer Note to Rev. Div. M.O.
Inspection of this site revealed 16 subjects screened, 15 randomized, 5 dropped, and 10 completed. Overall, there was sufficient documentation at this site to assure that all audited subjects did exist, and were available for the duration of the study and that all enrolled subjects received the assigned study medication had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocols and amendments. All subjects consented to the study.

Thus, all of the subjects at this site can be used for evaluation of Study Protocol # [redacted] in support of NDA 21-437.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS

G.D. Searle LLC
4901 Searle Parkway
Skokie, IL 60077

2. TELEPHONE NUMBER *(Include Area Code)*

(847) 982-4751

3. PRODUCT NAME

Eplerenone Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-437

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4208

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Donald Kyr	Director, Regulatory Affairs	November 8, 2001

FORM FDA 3397 (4/01)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 31 2002

Dear Dr.

Between April 15 and 19, 2002, Ms. Traci Armand, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol [redacted] of the investigational drug [redacted] (eplerenone), performed for G. D. Searle. During our initial contact, we learned that all of the original study documents had been destroyed during a hailstorm that damaged the records beyond salvation. We understand that the records were stored at the [redacted] and were, therefore, not under your direct control. However, we remind you that, as principal investigator, it is your responsibility to prepare and maintain study records. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent federal regulations governing your conduct of clinical investigations and the protection of human subjects. Because the original documents had been destroyed, the inspection was limited to photocopies of case report forms, laboratory reports, and electrocardiograms provided by the sponsor. We note that at the conclusion of the inspection, Ms. Armand presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not prepare and maintain adequate and accurate case histories (21 CFR 312.62(b)).

   a. There were no original source documents such as study worksheets and informed consent forms available.

   b. No electrocardiograms were available for subject 55583.

2. You did not conduct the study in accordance with the approved protocol (21 CFR 312.60).

   a. Subjects 55581, 55429, 55580, and 55583 were enrolled without using the revised, current inclusion and exclusion criteria.

   b. Ten of 23 subjects participating in the study after the implementation of amendment #3 (sexual dysfunction questionnaire) did not have the form completed or documentation of the reason that the form was not completed.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Armand during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN:
Field Classification: Refer to Center
Headquarters Classification:
_____1)NAI
__X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__X__records availability (01)
__X__failure to adhere to protocol (05)
Deficiency codes: 1, 5

cc:
HFA-224
HFD-110 Doc.Rm. NDA#21-437
HFD-110 Review Div.Dir. Throckmorton
HFD-110 MO Marciniak
HFD-110 PM Allis
HFD-47 c/r/s/ GCP File #10624
HFD-47 Shibuya
HFD-47 Storms
HFR-SE-450 Debo
HFR-SE-450 Wright
HFR-SE-450 Armand
r/d:**(RS)(6/5/02)**
reviewed:AEH:**(6/19/02)**
f/t:mb:**(6/19/02)**
o:**\RS\NDA21-437/**

Reviewer Note to Rev. Div. M.O.

Upon scheduling this inspection, the field investigator learned that all of the original study documents had been destroyed because of a destructive hailstorm more than two years prior to the inspection. Apparently, the documents were water damaged and could not be preserved. ——— the study record custodian, decided to destroy the records. The field investigator inspected photocopied case report forms and laboratory and EKG data provided by the sponsor and found a few protocol violations. However, because none of the data from this site was verifiable, none of the data from Dr. site should be considered in support of NDA 21-437.

I am concerned because Searle/Pharmacia did not report this data as unreliable. Dr. site did inform ——— of the destruction of the records soon after the hailstorm. We might consider contacting Searle to obtain a statement that the remainder of the data submitted in the application is verifiable.