CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-437

Chemistry Review(s)

Chemistry Review Cover Sheet

NDA 21-437

Eplerenone 25 mg, 50 mg and 100 mg Tablets

G.D. Searle LLC

N. Chidambaram Ph.D.
Cardio-Renal Drug Products (HFD-110)

Chemistry Review Data Sheet

1. **NDA**: 21-437

2. **REVIEW**: #2

3. **REVIEW DATE**: 08.27.02

4. **REVIEWER**: Nallaperumal Chidambaram

5. **PREVIOUS DOCUMENTS**: None

Previous Documents	Document Date
Original	November 28, 2001

6. **SUBMISSION(S) BEING REVIEWED**:

Submission(s) Reviewed	Document Date
Amendment (Fax)	08.14.02
Amendment (Fax)	08.19.02
Amendment (Fax)	08.23.02

7. **NAME & ADDRESS OF APPLICANT**:

Name:	G.D. Searle LLC
Address:	4901 Searle Parkway Skokie, IL 60077.
Representative:	Donald L. Raineri Director, Regulatory Affairs
Telephone:	(847) 982-4751

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) **Proprietary Name**: Inspra
b) **Non-Proprietary Name (USAN):** Eplerenone Tablets
c) **Code Name/# (ONDC only):**
d) **Chem. Type/Submission Priority (ONDC only):**
   - Chem. Type: 1
   - Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION**: N/A

10. **PHARMACOL. CATEGORY**: Treatment of Hypertension

11. **DOSAGE FORM**: Tablets

12. **STRENGTH/POTENCY**: 25 mg, 50 mg and 100 mg Tablets

13. **ROUTE OF ADMINISTRATION**: Oral

14. **Rx/OTC DISPENSED:** ✔ Rx ___ OTC

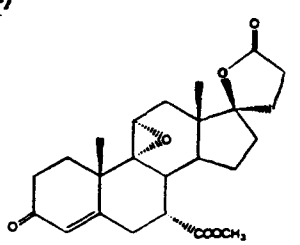
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]: No

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ-lactone, methyl ester, (7α,11α,17α)

$C_{24}H_{30}O_6$

414.50



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	4			
	III			1	Adequate	08.21.2002	
	III			1	Adequate	08.21.2002	
	III			3	Adequate	04.22.2002	
	III			3	Adequate	05.14.1999	
	III			3	Adequate	02.03.2002	
	III			3	Adequate	03.23.2000	
	III			3	Adequate	03.31.2001	
	III			3	Adequate	05.02.2002	
	III			1	Adequate	08.21.2002	
	III			3	Adequate	07.09.1998	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	Submitted on 10.24.1996

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	02.15.2002	B. Hartman
Pharm/Tox	N/A		
Biopharm	Acceptable	08.21.2002	R. Gabriel
LNC	N/A		
Methods Validation	Pending	08.21.2002	N. Chidambaram
OPDRA	Proprietary Name "Inspra" acceptable	07.17.2002	J. Fan
EA	Categorical Exclusion	08.21.2002	N. Chidambaram
Microbiology	N/A		

The Chemistry Review for NDA 21-437

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is NOT APPROVABLE from a chemistry, manufacturing and controls standpoint because:
The overall evaluation for CGMP compliance still reamins WITHHOLD. This recommendation is based on significant CGMP violations at the finished product manufacturing facility Searle & Co., Inc. (CFN 2623450) Caguas, Puerto Rico.

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) 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.

(b) 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.

(c) We recommend that individual synthetic iron oxides be listed in the description section of package insert.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Eplerenone is a white to off-white semi synthetic steroid with no characteristic melting point since it decomposes on melting. ———

Eplerenone is not soluble across the physiological pH range; however, it is

reasonably soluble in methanol, methyl ethyl ketone and is highly soluble in acetonitrile, benzyl alcohol and chloroform. Specified and potential impurities in the drug substance have been characterized. Eplerenone is an optically active compound with 8 chiral centers. Of the 8 chiral centers, five centers remain unchanged from the starting material and the other three 3 are introduced in a stereospecific manner. Two of the centers (C9 and C11) are involved in the formation of 9,11-epoxide. Epimerization at C9 and C11 is very sterically hindered and epimerization at these centers does not occur during synthesis. The remaining center (C7) can undergo epimerization to produce a pair of diastereoisomers (eplerenone and SC-70441). Two polymorphic forms (Form I and Form II) and multiple solvated forms of eplerenone have been observed. No hydrates of eplerenone are known. Form II is the principal form present in the drug substance and it has been shown to be a more thermodynamically stable polymorph at ambient temperature. Form I is controlled at low levels in DS specifications. Validated analytical methods were provided in the submission. Two year retest date was proposed but based on submitted data, 18 month retest date is acceptable.

Eplerenone drug product is formulated as an immediate release tablet formulation in three different strengths 25 mg (Yellow), 50mg (Pink) and 100 mg (Red) colored tablets. The drug product contains excipients that comply with compendial requirements. The drug product is manufactured by ——— The drug product is found to stable up to 12 months at 25°C/ ——— conditions and no degradants were observed. The proposed test methods are adequate. The acceptance criteria are adequate to ensure identity, assay, content uniformity. Eplerenone tablets are packaged in ——— bottles, unit dose blisters and foil pouches. All packaging components are made of standard packaging components and based on stability, deemed adequate to protect the drug product through its shelf life. Based on 95 percent confidence intervals for mean assay value, the applicant predicts at least ——— expiration dating period. However, based on test data, an expiry-dating period of 18 months is acceptable. Validated analytical methods were provided in the submission.

The trade name ——— initially proposed by the applicant was found not acceptable by the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety. But the other proposed name **Inspra** was found acceptable.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used orally either alone or in combination with another anti-hypertensive agent. The recommended starting dose is 50 mg administered once daily. This may be increased to either 100 mg or 200 mg.

C. Basis for Approvability or Not-Approval Recommendation

This application is NOT APPROVABLE because:
The overall evaluation for CGMP compliance still remains WITHHOLD. This recommendation is based on significant CGMP violations at the finished product manufacturing facility Searle & Co., Inc. (CFN 2623450) Caguas, Puerto Rico.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Nallaperumal Chidambaram/Date:
ChemistryTeamLeader Kasturi Srinivasachar/Date
ProjectManager Daryl Allis/Date

C. CC Block

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G.D. Searle LLC

N. Chidambaram Ph.D.
Cardio-Renal Drug Products (HFD-110)

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3. **REVIEW DATE**: 08.21.02

4. **REVIEWER**: Nallaperumal Chidambaram

5. **PREVIOUS DOCUMENTS**: None

Previous Documents	Document Date

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c) **Code Name/# (ONDC only):**
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   - Chem. Type: 1
   - Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION**: N/A

10. **PHARMACOL. CATEGORY**: Treatment of Hypertension

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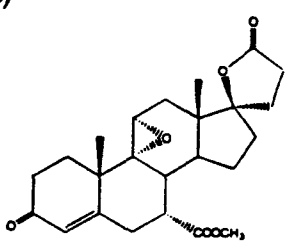

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(2) CMC deficiencies with respect to drug substance and finished product listed at the end of the review in the draft letter need to be resolved in a satisfactory manner.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

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(2) There are some CMC deficiencies with respect to drug substance synthesis and specifications, drug product specifications. Those deficiencies are listed at the end of the review in the draft letter and they need to be resolved in a satisfactory manner.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Nallaperumal Chidambaram/Date:
ChemistryTeamLeader Kasturi Srinivasachar/Date
ProjectManager Daryl Allis/Date

C. CC Block

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information

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

/s/

Nallaperumal Chidambaram
8/27/02 10:09:40 AM
CHEMIST

Kasturi Srinivasachar
8/27/02 10:23:41 AM
CHEMIST

ENVIRONMENTAL ASSESSMENT
CLAIM FOR A CATEGORICAL EXCLUSION

Under the provisions of 21 CFR 25.31(b), action on a New Drug Application (NDA) are categorically excluded and, therefore, ordinarily do not require the preparation of an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. G.D. Searle LLC, Subsidiary of Pharmacia Corp., claims a categorical exclusion to the EA requirements in accordance with 21 CFR 25.31(b) for eplerenone as the total annual sales for all indications are projected to be significantly less than [redacted] G.D. Searle LLC, is not aware of the existence of any extraordinary circumstances that would require the preparation of an EA. Also, G.D. Searle LLC does not have any new information to indicate that eplerenone may be toxic to organisms in the environment at the expected levels of exposure.

1. Date
October 09, 2001

2. Name of Applicant

G.D. Searle *LLC*
Subsidiary of Pharmacia Corp.
4901 Searle Parkway
Skokie, Illinois 60077

Contact: Daniel E. Sullivan, PhD
Tel. (616) 833-0394

3. List of Preparers

Daniel E. Sullivan, Ph.D. Director of Environmental Affairs	Ph.D. Environmental Engineer with twenty-two years in chemical fate and effect evaluations, WWTP operations, and regulatory compliance.

4. Certification
The undersigned certifies that the information presented is true, accurate, and complete to the best knowledge of G.D Searle LLC.

Daniel P Sullivan — OCTOBER 9, 2001

Daniel E. Sullivan, Ph.D. — Date