CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-437

Medical Review(s)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: September 6, 2002

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader Division of Cardio-Renal Drug, Products HFD-110

THROUGH: Dr. Douglas Throckmorton, Director, Division of Cardio-Renal Drug, Products HFD-110

To: Dr. Robert Temple, Director, ODE I.

Subject: Approvability of NDA 21-437 Eplerenone Tablets [Inspra®] (Sponsor: G.D. Searle LLC).

Documents Used in the preparation of this review:

Chemistry reviews By Dr. Nallaperumal Chidambaram; dated 8.21.02, 8.22.02; and 8.26.02 (these were signed off on 8.27.02, 8.27.02 and 9.3.02).

Clinical pharmacology and biopharmaceutics review by Dr. Gabriel Robbie dated 8.23.02.

Pharmacology review by Dr. Elizabeth Hausner dated 1.15.02.

Statistical evaluation of carcinogenicity by Dr. Roswitha Kelly dated 1.15.02.

Proprietary name review by Jennifer Fan, Pharm.D., dated 11.21.01. DMETS proprietary labeling review dated 8.28.02 by Charles Hoppes, R.Ph., M.P.H.

Biometrics review by Dr. John Lawrence dated 11.28.01.

Medical officer review by Dr. Thomas Marciniak dated 1.24.02.

Additional: Minutes of meeting dated 11.28.01, CAC minutes dated 11.29.01

Overall Conclusions:

This memo 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.

Overview:
My edited labeling are attached. I have incorporated the comments made by the reviewers. I have also considered the labeling comments of Cheryl D. Cropp, Pharm.D., of DDMAC in the memo dated 9.2.02.

Chemistry:
The chemists have recommended approval of eplerenone with an expiration date of eighteen months. The following comments from Dr. Chidambaram's review should be incorporated into 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 the proposed name to be identical to one of 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) 9,11 α-Epoxy-17-hydroxy-3-oxo-17α -pregn-4-ene-7α,21-dicarboxylic acid, γ -lactone, methyl ester.
(c) Individual synthetic iron oxides should be listed in the description section of the package insert.

Inspections and Audits:
Inspections have been successfully completed. DSI audits are completed, and raised no impediments to approval. The study records of one study site (site # 003) of study #010 were unavailable. They were apparently irretrievably water damaged and unusable. The outcome of this study, however, did not materially change when this study site was excluded.

Trade name review:
DMETS has approved the Trade name Inspra®. DMETS raises the following issues and comments:

- 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.
- Container label (unit dose)
  - Increase the prominence of the established name so that it is at least half the size of the proprietary name
  - 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.
- 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.

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

Pediatric Studies:

A deferral of pediatric studies was granted.

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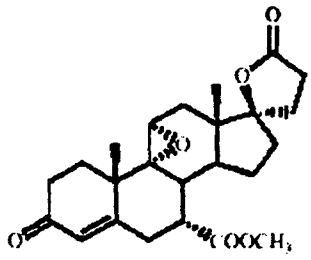
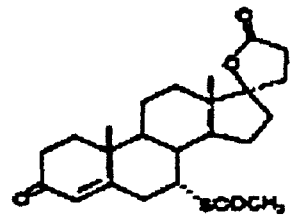
Review:

Eplerenone is structurally similar to spironolactone (See Figure 1).

Figure 1



Eplerenone



SPIRONOLACTONE

In rat, eplerenone binds to the mineralocorticoid receptors and inhibits the binding of aldosterone. Using recombinant human steroid receptors, eplerenone inhibited mineralocorticoid receptor transcriptional activity in a concentration dependent manner, with an IC50 of 0.3 nM.

In rats, eplerenone seems to highly selectively in its bind to the mineralocorticoid receptor as compared to its binding to other steroid receptors (androgen, glucocorticoid and progesterone). Estrogen receptor binding was not specifically tested, but since high doses of eplerenone did not affect fertility, a strong estrogen receptor interaction with eplerenone is unlikely. There is less convincing data, however, from humans about the selectivity of eplerenone for the mineralocorticoid receptor relative to other steroid receptors.

Since aldosterone acts by de-repressing or inducing aldosterone-induced proteins, the time-course of eplerenone's effect may be dissociated from acute serum concentrations of the drug.

Eplerenone's Biopharmaceutical characteristics were excerpted from Dr. Gabriel Robbie's review. Eplerenone exists in aqueous solution in equilibrium with its inactive lactone form, in a ratio of >19:1. When administered to healthy normal individuals, eplerenone is rapidly absorbed; T_{max} occurs at approximately 1.5 hours. Peak concentrations of eplerenone after a single 100-mg dose were approximately 2000 ng/ml (4.8 uMol), with approximate dose-proportionality maintained in the dose range of 50-300 mg. At doses higher than 300 mg, the concentrations were lower than anticipated based on the proportional increase in dose.

Since there was no intravenous formulation available for study, the absolute bioavailability of eplerenone is unknown. Potent CYP3A4 and CYP2C9 inhibitors, however, increase C_{max} by approximately 2 and 1.4 fold, respectively. Consequently, it is likely that eplerenone's bioavailability is less than 50%. The 3 major metabolites of eplerenone; 6-β-OH-, 6-β, 21-OH-, and 21-OH eplerenone account for slightly more than 60% of the administered dose. All these metabolites are biologically inactive with respect to mineralocorticoid receptor activity. Little eplerenone is excreted unchanged. The terminal half-life of eplerenone is approximately 4-6 hours. Protein binding is moderate (approximately 50% in humans).

Key findings of the pre-clinical pharmacology of eplerenone, as reviewed by Dr. Hausner, include adrenal zona glomerulosa hypertrophy in both rodents and dogs during chronic treatment. There was adaptive induction of CYP450 with hepatocellular hypertrophy found in rats and mice (not dogs) treated with eplerenone. The increase in the metabolic enzyme systems altered the metabolism of thyroid hormone leading to thyroid hyperplasia (limited to rodents). Chronic progressive nephropathy was a key observation in a large fraction of female rats. Female rats differ from males in the processing of eplerenone with higher total body exposure than male rats and the difference in exposure may account for the differences between male and female rats with respect to the incidence of nephropathy. Prostatic atrophy was the most prominent observation in male dogs.

There were no carcinogenicity findings deemed to be clinically relevant by the CAC executive committee in the outcomes of the 26-week p53 mouse, 2-year carcinogenicity and 2-year restricted diet rat studies. There, was, however, a finding of an increase in renal tumors in rats limited to the high dose female group in the 2-year carcinogenicity study. The relevance of this finding was discounted for the following reasons.

- The event rate was within the extremes of lab experience.
- The events were correlated with chronic progressive nephropathy and likely, therefore, the consequence of the nephropathy. Other drugs that promote chronic progressive nephropathy are also associated with renal tumors, with no obvious correlation during clinical use.
- Serial sectioning of kidneys failed to show additional adenomas or hyperplastic foci, as have been demonstrated in known renal carcinogens.

Eplenrenone was not genotoxic in the Ames, mouse lymphoma, chromosomal aggregation (CHO cells), rat micronucleus assays and in vivo/in vitro unscheduled DNA synthesis in rat primary hepatocyte cultures.

Dr. Marciniak's review is an excellent overview and analysis of the clinical data supporting the approval of eplerenone for the treatment of hypertension. The clinical experience consists of thirteen controlled clinical studies as well as an open label extension study. These studies enrolled a total of 4,908 patients of which 3,106 patients received at least one dose of eplerenone. The remainder of these patients received either placebo or one of several positive controls.

Two of these studies are relevant to eplerenone's approval. Study 010 was a double blind, placebo-controlled, dose ranging study with a concurrent positive control. Subjects received placebo (BID), eplerenone at doses of 50, 100 or 400 mg daily; eplerenone at 25, 50 or 200 mg BID; or spironolactone at a dose of 50-mg BID. Three hundred ninety seven subjects were randomized and evaluated (this excludes study site #003 for which the CRFs were unavailable). The primary measure of efficacy was the change from baseline in cuff sitting DBP at trough after 8 weeks of treatments. Additional measurements reflecting blood pressure effects were standing measurements of diastolic and systolic blood pressures as well as 24 hour ABPM profiles.

Study 049 was a placebo-controlled, double blind, dose-ranging study in subjects with mild-moderate hypertension (DBP 95 to 110 mm Hg). A total of 400 subjects were randomized in a 2: 1: 2: 2: 2 ratio to placebo or eplerenone at doses of 25, 50, 100 and 200 mg. The primary metric of interest was seated cuff trough diastolic blood pressure at the end of week 12. Additional measurements relevant to blood pressure control were seated systolic blood pressures and ABPM profiles at the end of 12 weeks of treatment.

The results of the two pivotal studies are shown below for supine systolic and diastolic measurements (figures 2 and 3, respectively) For both studies, there appears to be dose-related reductions in these blood pressure measurements. The shape of the blood pressure effect versus dose was curvilinear (Dr. Lawrence's review); the coefficient of the quadratic term was significant for the BID dosing regimen (not the QD regimen) of study 049 and the DBP measurements of study 010. Dr. Robbie fit the combined results (DBP) of the two studies to an E_{max} model. The estimated E_{max} for diastolic blood pressure reduction was 6.3% of a baseline value of 99-mm Hg. The daily dose, at which half-maximal effect was observed, was approximately 40 mg. Based on these analyses, doses higher than 200 mg daily is likely to yield only modest (but still measurable) additional blood pressure effects.

Once a day dosing is supported by study 010 and 049 during which ambulatory blood pressure was recorded (Figures 4-7; excerpted from Dr. Marciniak's review). Figures 4 and 5 depict the results of study 010 and compares the effect of the BID doses compared to the same dose given once daily, with corresponding placebo for diastolic and systolic blood pressure measurements, respectively. The effect of spironolactone 50-mg BID is included only for the diastolic measurements. Figure 6 and 7 depict the results for study 049 for the diastolic and systolic ambulatory effects, respectively.

Figure 2

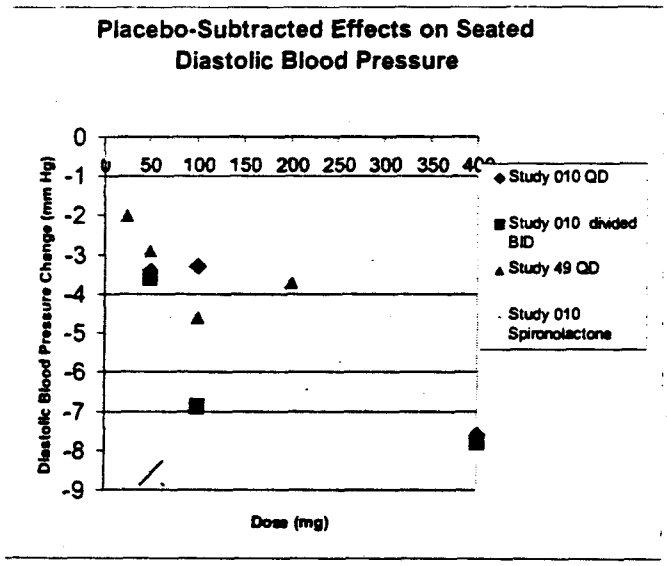
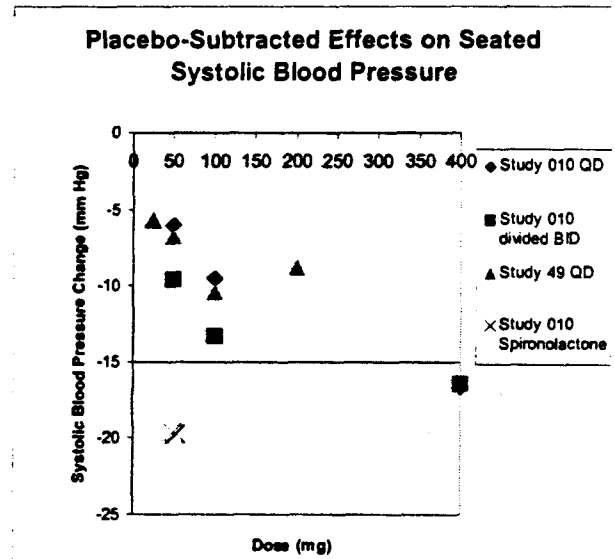


Figure 3



Blood pressures measurements during the entire 24-hour period, are well controlled either when eplerenone was administered as once a day (studies 010 and 049) or twice a day (study

010); when considering either diastolic or systolic blood pressures. The results also suggest that the same total daily dose when administered BID is slightly superior to the same dose administered once daily.

Figure 4 Study 010 ambulatory DBP

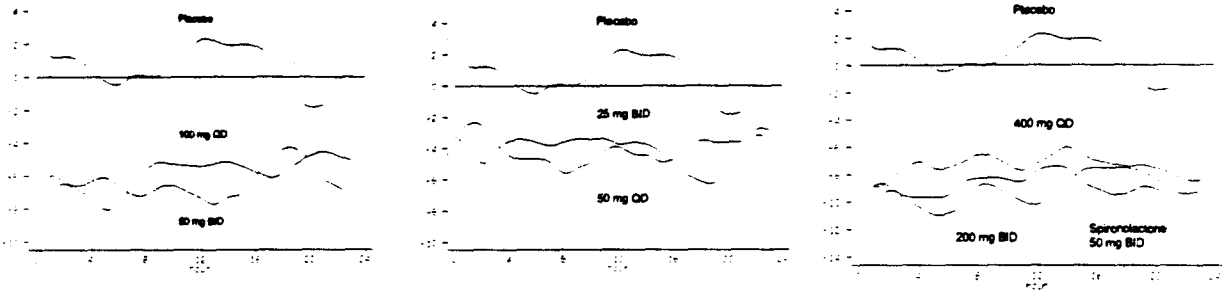


Figure 5 Study 010 ambulatory SBP

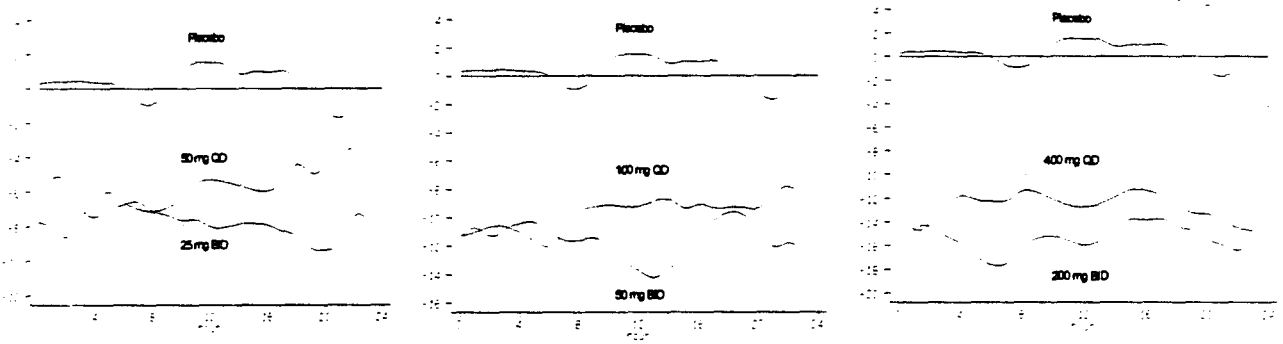


Figure 6 Study 049 ambulatory DBP

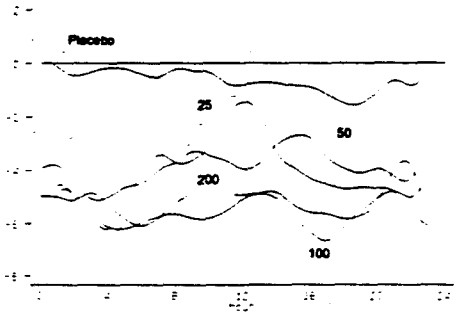
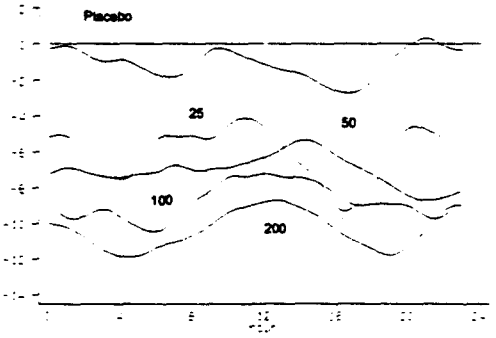


Figure 7 Study 049 ambulatory SBP



The vast majority of the blood pressure effect of eplerenone is observed by two weeks of treatment (study numbers 010 and 049, see page 52 of Dr. Marciniak's review). There is a suggestion of a small additional blood pressure effect at 4 weeks. Dosing increases should be predicated on blood pressure responses after at least two weeks on fixed doses of eplerenone.

With respect to the persistence effect over time, there was no appreciable waning of effect during long-term follow-up (see graph on page 54 of Dr. Marciniak's review). Withdrawal for loss of control (17% of those enrolled), as well as the addition of other antihypertensive medications for patients, whose blood pressure was inadequately controlled, detracts from any strong conclusion as to the persistence of eplerenone's antihypertensive effect. A randomized withdrawal study was not performed among those adequately treated with eplerenone. The one study where down-titration was attempted (study 016), was a positive controlled study (enalapril) antihypertensive drugs were down-titrated in all patients by only one dose level (e.g. eplerenone 200 to 100 mg daily; 100 to 50 mg daily; or enalapril 10 to 5 mg daily). No clear estimate of the residual blood pressure effect can be ascertained from the results of this study.

Eplerenone has been used in conjunction with diuretics, ACE-inhibitors, angiotensin II blockers, beta-blockers and calcium channel blockers. The factorial study (015), though unsuccessful in demonstrating a statistically significant additive effect of eplerenone with hydrochlorothiazide, was at least suggestive that there may be additive effects of the concurrent use of eplerenone with a diuretic.

Comparison with spironolactone: There are two sets of data for which a comparison of eplerenone can be made with aldactone. In study 010, one randomized group was treated with spironolactone at a fixed dose of 50-mg BID (approved spironolactone dose is 50-100 mg daily for use in hypertension). The effect of eplerenone at it's the highest use dose (400 mg daily or 200 mg BID) only approximated the blood pressure effect of the 50-mg BID dose of spironolactone (see Figure 4).

The second study was Study 018, 141 subjects with primary hyperaldosteronism with a wash-out diastolic blood pressure of between 95-119 mm Hg and a SBP of < 200 mm Hg, were randomized in a 1: 1 ratio to eplerenone at a dose of 100 mg or spironolactone at a starting dose of 75 mg. If the effect of blood pressure was inadequate, the doses were upward titrated at weeks 4, 8 or 12 to a maximum dose of 300 mg daily for eplerenone or 225 mg daily for spironolactone (the dose of spironolactone is 100-400 mg daily for patients with hyperaldosteronism). The mean decrease at week 16 for trough seated DBP was –5.6 mm Hg for eplerenone and –12.5 mm Hg for spironolactone. Therefore, in a primary hyperaldosteronism population with mild-moderate hypertension, a dose of 225-mg daily of spironolactone was superior to that of 200-mg daily dose of eplerenone.

Populations: Eplerenone appears to be an antihypertensive medication in blacks, but whether the magnitude of its effect in this population is equivalent to that in non-blacks is unclear.

Study 020 was a placebo-controlled study comparing losartan with eplerenone. Subjects with mild to moderate hypertension (DBP 95-109, SBP < 180 mm Hg) were randomized to receive

placebo, losartan or eplerenone. Blacks were randomized in an approximately 2:1 ratio compared to whites. Within each study center subjects were stratified based on race. The initial dose of eplerenone and losartan was 50 mg daily. Upward titration was based on blood pressure response (if BP was > 140/90 the dose was increased) at weeks 4 and 8. The increase in losartan dose was limited to 100 mg daily. The increase in eplerenone dose was to 100 and 200 mg daily. Pivotal blood pressure measurements were performed at week 16. The effect for blacks treated with eplerenone were statistically greater than blacks treated with placebo or with losartan. Relative to Caucasians, the effects appear comparable, but the confidence intervals are quite generous.

Study 019 was a positive controlled study comparing the effect of losartan and eplerenone among patients with low renin hypertension (supine renin < 25 pg/ml). Slightly over 30% of those enrolled were black and these subjects, though not stratified, were equally allocated between losartan and eplerenone. Subjects were titrated to effect. The initial dose of eplerenone was 100 mg daily; that for losartan was 50 mg daily. Upward titration was provoked by a DBP >90 mm Hg. Follow-up visits scheduled for week 4. If blood pressure was not adequately controlled the dose of eplerenone and losartan could be increased to 200 and 100 mg daily, respectively. Follow-up visits at week 8 and later would allow the addition of hydrochlorothiazide at doses of 12.5 and 25 mg. The following results were culled from Dr. Marciniak's review for the effect at week 8 (before the addition of diuretics) suggest a lesser effect in blacks compared to non-blacks for both eplerenone and losartan.

Table 1 Effect on diastolic blood pressure study 019 and effect of race

Drug	Race	DBP (week 8)	SBP (week 8)
Eplerenone	Black	-7.1	-12.4
	Non-black	-12.0	-19.3
Losartan	Black	-5.7	-8.7
	Non-black	-7.4	-12.6
P-value race		0.014	0.021
p-value drug		0.011	0.008

Dr. Lawrence, the FDA biostatistician, analyzed the effect of race in the two pivotal studies. In study 049, approximately 21% of those enrolled were black. In study 010 approximately 20% of those enrolled were black. Dr. Lawrence concluded, "there did not appear to be a significant differences in effect across subgroups".

In summary, there appears to be no doubt that hypertensive blacks are responsive to eplerenone. Whether blacks are equivalently responsive to eplerenone as Caucasians cannot be ascertained by the totality of the data.

With respect to other subgroup analyses, age (> 65 and < 65 years) and gender do not appear to interact with blood pressure effect of eplerenone.

Safety:

There were a total of 3,106 patients who received at least one dose of eplerenone. Of these, 690 patients were exposed for more than six months and 106 patients were exposed for more than one-year. Total exposure was 1081 patient-years. With the exception of events that often require longer duration of treatment, such as gynecomastia, the duration of exposure is more than adequate information to label this drug for safety.

The duration of exposure by dose is shown below (page 73 of Dr. Marciniak's review). Safety of eplerenone was primarily derived from doses of 200 mg and lower.

Table 2. The duration of exposure for those who received eplerenone with or without other antihypertensives as well as those who received eplerenone as monotherapy. Excludes the long term-extension sudy.

	Eplerenone						
Exposure (Days)	**25 mg**	**50 mg**	**100 mg**	**200 mg**	**300 mg**	**400 mg**	**Overall[a]**
Eplerenone Only							
1-15	5	684	504	198	1	4	107
16-30	14	358	339	230	4	0	78
31-60	52	235	228	166	19	78	713
61-90	41	131	149	148	4	22	459
91-120	3	62	81	64	0	0	324
121-150	2	11	26	87	0	0	46
151-180	26	66	23	15	0	0	157
181-270	15	35	47	112	0	0	92
271-336	0	40	46	45	0	0	194
337-360	0	4	10	11	0	0	95
> 360	0	14	0	1	0	0	69
No. Treated	158	1645	1453	1077	28	104	2334
Eplerenone Plus Other Active Medication (Coadministration Background, or Additional Antihypertensive)							
1-15	13	939	640	58	1	4	146
16-30	18	419	409	122	4	0	107
31-60	127	461	305	271	19	78	954
61-90	57	158	146	180	4	22	533
91-120	3	62	91	82	0	0	361
121-150	2	11	26	183	0	0	63
151-180	26	68	23	42	0	0	252
181-270	15	35	47	235	0	0	189
271-336	0	40	46	104	0	0	288
337-360	0	4	10	41	0	0	107
> 360	0	14	0	1	0	0	106
No. Treated	261	2211	1743	1319	28	104	3106

Source: Table T3.8.
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 025, 026, and 049.
[a] Represents patients irrespective of dose and is not necessarily the sum of individual eplerenone columns.

The demographics of those enrolled into the study shown below taken from page 72 of Dr, Marciniak's review). There was adequate exposure to racial minorities, women and aged.

Table 3. Demographics of those enrolled into the clinical development program of eplerenone (excludes long-term safety study).

Characteristic	Placebo		Eplerenone Monotherapy		Eplerenone Coadministration Therapy		Active Comparators	
No. treated	375		1748		772		1422	
Age (years)								
< 35	13	(3.5)	60	(3.4)	32	(4.1)	40	(2.8)
35-44	59	(15.7)	270	(15.4)	96	(12.4)	170	(12.0)
45-54	151	(40.3)	515	(29.5)	238	(30.8)	380	(26.7)
55-64	95	(25.3)	533	(30.5)	218	(28.2)	451	(31.7)
65-74	45	(12.0)	305	(17.4)	155	(20.1)	303	(21.3)
> 74	12	(3.2)	65	(3.7)	33	(4.3)	78	(5.5)
Mean		53.2		55.1		55.6		56.8
Range		20-80		19-89		19-89		19-91
Ethnicity								
Asian	4	(1.1)	19	(1.1)	11	(1.4)	13	(0.9)
Black	152	(40.5)	309	(17.7)	58	(7.5)	209	(14.7)
Caucasian	192	(51.2)	1263	(72.3)	597	(77.3)	1082	(76.1)
Hispanic	26	(6.9)	136	(7.8)	102	(13.2)	112	(7.9)
Other	1	(0.3)	21	(1.2)	4	(0.5)	6	(0.4)
Gender								
Female	177	(47.2)	794	(45.4)	363	(47.0)	666	(46.8)
Male	198	(52.8)	954	(54.6)	409	(53.0)	756	(53.2)

The cumulative duration of exposure for eplerenone monotherapy, eplerenone in combination with other antihypertensive medications, placebo and other therapies is shown below. There were 2,520 patients exposed for a total of 665.8 patient years exposed to eplerenone as mono or in combination therapy.

Table 4.Duration of exposure during the eplerenone development program (excludes long-term safety).

	Eplerenone as *monotherapy*	**Eplerenone as *combination***	**Other active**	**Placebo**	**Any eplerenone**	**No eplerenone**
N=	**1748**	**772**	**1422**	**375**	**2520**	**1797**
PEY*	**496.9**	**168.9**	**437.6**	**78.9**	**665.8**	**516.5**
*** PEY= Patient Exposure Years.**						

There were five deaths during the clinical studies or shortly after the competition of the study; four during eplerenone (with or without concomitant antihypertensive drugs) and one during enalapril therapy.

Serious adverse events, events leading to discontinuation, and overall adverse events of > 2% incidence (pages 74, 83 and 90 as described in Dr. Marciniak's review) indicate that with the exception of hyperkalemia, the safety profile of this drug is relatively benign.

Laboratory, limited to chemistries:
The dose-related changes in chemistries (page 98 of Dr. Marciniak's review) are shown below.

Eplerenone treatment was associated with several dose-related changes in chemistry values. In particular potassium, sodium, creatinine, BUN, uric acid, cholesterol, triglycerides, SGOT, SGPT and GGTP were altered in an apparent dose-related manner.

Table 7. Mean baseline values and (change) in chemistry values from baseline –placebo controlled clinical trials. Dose reflects total daily dose and is a combination of the QD and BID dosing regimens.

Laboratory Test (unit)	Placebo (N=194)		Eplerenone 25 mg (N=97)		50 mg (N=245)		100 mg (N=193)		200 mg (N=139)		400 mg (N=104)	
Total Bilirubin (umol/L)	9.6	(0.3)	8.1	(0.5)	10.3	(-0.1)	10.8	(-0.5)	8.8	(-0.2)	12.2	(-0.3)
Direct Bilirubin (umol/L)	2.3	(0.0)	N/A	N/A	2.5	(-0.1)	2.5	(-0.1)	N/A	N/A	2.4	(-0.1)
Indirect Bilirubin (umol/L)	8.8	(0.1)	N/A	N/A	9.6	(0.1)	9.7	(-0.3)	N/A	N/A	9.8	(-0.2)
Alkaline phosphatase (U/L)	72.2	(1.2)	71.5	(1.5)	71.2	(-0.5)	72.1	(0.4)	72.1	(0.3)	73.7	(-0.4)
AST/SGOT (U/L)	23.7	(-0.3)	23.1	(0.0)	22.7	(-0.5)	21.1	(0.1)	23.3	(1.4)	18.9	(1.9)
ALT/SGPT (U/L)	24.9	(0.6)	24.3	(0.5)	23.8	(0.8)	23.0	(1.3)	25.2	(1.2)	21.7	(4.7)
LDH (U/L)	158.2	(-11.6)	N/A	N/A	152.1	(-3.8)	149.1	(-2.3)	N/A	N/A	146.9	(-6.8)
GGT (U/L)	33.5	(1.5)	29.1	(1.5)	36.5	(2.9)	32.9	(3.7)	29.8	(3.2)	34.5	(11.4)
Creatine Kinase (U/L)	237.4	(-93.2)	153.8	(-17.5)	139.1	(-13.4)	135.4	(-8.7)	135.0	(5.4)	126.0	(-22.8)
Creatinine (umol/L)	78.6	(-0.4)	76.5	(-0.5)	82.9	(1.2)	82.8	(0.5)	73.9	(2.0)	95.0	(2.5)
BUN (mmol/L)	5.15	(-0.08)	5.24	(0.03)	5.09	(0.39)	4.97	(0.39)	5.34	(0.46)	5.17	(0.79)
Sodium (mmol/L)	141.1	(0.1)	140.1	(0.2)	141.1	(-0.6)	141.1	(-0.9)	141.1	(-1.1)	140.9	(-1.8)
Potassium (mmol/L)	4.27	(-0.02)	4.28	(0.08)	4.22	(0.14)	4.23	(0.09)	4.25	(0.19)	4.19	(0.36)
Chloride (mmol/L)	104.9	(-0.2)	104.2	(0.3)	105.1	(-0.2)	105.5	(-0.6)	105.0	(-0.7)	105.2	(-1.1)
Bicarbonate (mmol/L)	25.5	(-0.1)	25.6	(-0.5)	25.7	(-0.9)	24.7	(-1.0)	25.6	(-0.9)	N/A	N/A
Uric Acid (umol/L)	331.9	(4.8)	354.9	(10.3)	340.2	(15.8)	331.4	(18.0)	341.5	(19.1)	306.7	(24.2)
Glucose (mmol/L)	5.72	(0.01)	5.70	(0.08)	5.74	(0.02)	5.82	(0.16)	5.62	(0.22)	5.85	(0.11)
Total Protein (g/L)	72.7	(0.7)	73.1	(0.2)	72.4	(0.4)	72.4	(0.4)	73.2	(0.7)	70.6	(1.9)
Albumin (g/L)	41.2	(0.4)	40.3	(0.3)	40.9	(0.2)	40.9	(0.1)	40.8	(0.1)	41.1	(0.4)
Calcium (mmol/L)	2.326	(0.023)	2.303	(0.016)	2.345	(0.004)	2.354	(0.009)	2.309	(0.030)	2.349	(0.051)
Inorganic Phosphorus (mmol/L)	1.092	(0.021)	1.101	(0.012)	1.108	(0.019)	1.094	(0.001)	1.086	(0.032)	1.062	(0.009)
Magnesium (mmol/L)	0.845	(-0.002)	0.838	(0.004)	0.845	(-0.011)	0.835	(-0.018)	0.841	(-0.018)	0.847	(-0.011)
Cholesterol (mmol/L)	5.235	(0.098)	5.310	(-0.038)	5.387	(0.086)	5.191	(0.086)	5.217	(0.126)	5.319	(0.244)
Triglycerides (mmol/L)	1.687	(0.082)	1.798	(0.111)	1.976	(0.163)	1.992	(0.085)	1.921	(0.103)	1.682	(0.404)

Source. Table T11.2.2
Includes Studies 010. 015. and 049.
Data are expressed as mean Baseline (mean change to Final Visit).
N/A=not applicable

Specific Adverse events:
Hyperkalemia: There were 36 withdrawals attributed to hyperkalemia. Thirty of these were either on eplerenone as monotherapy or combination therapy. The other hyperkalemia withdrawals were scattered through placebo treated and other active treated subjects. The potassium values at the time of withdrawal were between 5.5 and 6.6 mmol/L. Values of greater than 7, however, were occasionally observed.

During clinical trials laboratory assessments were scheduled at two weeks to monthly intervals, and this frequency of monitoring is appropriate, particularly for subjects with factors predisposing to elevated potassium levels. Such factors include higher doses, diabetics, concomitant use of enalapril (ACE-I) and subjects with elevated creatinine. The timing of the onset of hyperkalemia was variable. Once K+ levels > 5.5 were subjects were frequently continued on therapy without altering the dose. Among these subjects there did not appear to be progressive increases in potassium over time, often despite continued.

Hyperkalemia was more frequently observed during combination therapy with enalapril particularly in the diabetic population with proteinuria (study 021).

Sex Hormone Related Effects: There were 10 subjects who discontinued for sex-hormone related events during clinical studies. Six of these subjects were treated with spironolactone at doses of 75-222 mg daily. There were four subjects who were treated with eplerenone either alone or in combination with sex-hormone related adverse events leading to dropouts (two subjects with gynecomastia, one each with impotence, orchitis and menstrual disorder). Breast-related adverse events are listed on page 132 of Dr, Marciniak's review. There were 14 such events described as pain, swelling, mass or tenderness while subjects were treated with eplerenone, either as monotherapy or in combination with other hypertensives. There were 12 such events during spironolactone treatment.

Liver Dysfunction: Hepatic enzyme related adverse events were modestly more frequent in the eplerenone treated subjects than placebo or comparator, 2.1%, 1.7%, and 1.3%, respectively. Most subjects with elevated liver functions re-approached baseline values despite continued therapy, or upon discontinuation of treatment.

Other: Dr. Marciniak's review raises the issue of the effect of eplerenone on the fibrinolytic system. Median plasminogen activator inhibitor (PAI) was numerically increased relative to comparator treatment in five positive controlled or open-label studies, but only achieved nominal statistical difference in 2 studies. The magnitude in all studies was modest 2-20%. On the other hand, eplerenone also slightly (approximately 5%) increases tissue plasminogen activator. Since the effect on the clotting system is different, PAI predisposing to thrombosis and t-PA to bleeding, the net effect of these changes is obscure.

Safety Summary: There was more than adequate exposure to assess the safety of eplerenone for the treatment of hypertension. Dose limiting adverse events was hyperkalemia.

Labeling Comments:

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

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/s/

Abraham Karkowsky
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MEDICAL OFFICER

Executive CAC
Date of Meeting: July 9, 2002
Mouse/Rat Carcinogenicity Study

Committee:

Joseph Contrera, Ph.D., HFD-900, Acting Chair
Barry Rosloff, Ph.D., HFD-120, Alternate Member
Jim Farrelly, Ph.D. HFD-530, Alternate Member
Pat Harlow, Ph.D. standing in for Al DeFelice, Ph.D. Team Leader
Elizabeth Hausner, D.V.M., HFD-110 Presenting Reviewer

Author of Draft: Elizabeth Hausner

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA 21437
Drug Name: Eplerenone
Sponsor: Pharmacia
This was a second meeting of the Exec CAC regarding the carcinogenicity findings for this drug. Eplerenone has tested negative in all genotoxicity tests (Ames assay, mouse lymphoma assay, chromosomal aberration assay (CHO cells), rat micronucleus assay and in vivo/in vitro unscheduled DNA synthesis in rat primary hepatocyte cultures.

With prior concurrence of the CAC, the sponsor conducted a 26-week study using p53 mice. There were no significant carcinogenicity findings.

In a standard 2-year rat study, the incidence of 2 renal tumors in the HD females versus 0 incidence in the control females prompted the Exec CAC and the Division to request further information from the sponsor. The additional information included blinded re-reading of the existing slides and creation of additional slides by step sectioning the tissues with blinded evaluation. The sponsor was asked to provide step sectioning and blinded evaluation of a restricted diet study also. The sponsor complied with this, had the slides peer reviewed by two outside pathologists and then examined by a pathology working group.

Executive CAC Recommendations and Conclusions:

After evaluation of the additional information submitted by the sponsor the committee concluded that the renal neoplasia in HD female rats was not a biologically significant finding.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

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/Division File, HFD-110
/A. DeFelice, Ph.D. HFD-110
/E. Hausner, D.V.M. HFD-110
/Daryl Allis, HFD-110
/ASeifried, HFD-024

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/s/

Joe Contrera
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Executive CAC
Date of Meeting
Mouse/Rat Carcinogenicity Study

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Robert Osterberg, Ph.D., HFD-520, Alternate Member
Al DeFelice, Ph.D., HFD-110, Supervisor
Elizabeth Hausner, D.V.M., Presenting Reviewer

Author of Draft:Elizabeth Hausner

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND # [redacted]
Drug Name: Eplerenone
Sponsor: Pharmacia (G.D. Searle Inc.)
Eplerenone is an anti-mineralocorticoid to be used in states of excess aldosterone levels. Due to structural similarity to spironolactone the drug was expected to produce tumors in rodents.

Mouse Carcinogenicity Study: A 26-week p53 +/- study was conducted at doses of 100, 300 and 1000 mg/kg/day p.o. There were 15 mice/sex/group. P-cresidine was the positive control used. Malignant lymphoma was reported in the HD eplerenone groups: 2/15 M and 1/15 F. The sponsor reports a historical control range of 4/45 lymphomas with 3/15 occurring in the female p53 $^{+/-}$ control group of one study. Hyperplasia (typical or atypical) was not reported in the histopathology records. CDER statistical analysis is pending.

Rat Carcinogenicity Study: Sprague-Dawley rats were dosed with 20, 75 or 250 mg/kg/day of eplerenone. There were increased incidences of thyroid follicular cell adenoma: Males: 1/85(C), 4/85 LD, 10/85 MD (p=0.003)and 9/85 HD (p=0.003). Females: 6/85 HD(p=0.000). Follicular cell adenoma and carcinoma combined, in males were: 2/85(C), 5/85 LD, 11/85 MD(p=0.011) and 9/85 HD(p=0.011). In females, the combined incidences were 1/85(C), 1/85 LD, 1/85 MD and 7/85 HD (p= 0.002). There was also a finding of renal tubular carcinoma in the females, 2/85, in only the HD group. In the males, 2/85 control animals were found to have this neoplasia. Incidence and severity of chronic progressive nephropathy increased in drug-treated females with the HD group most affected. The sponsor performed ancillary studies to demonstrate induction of T4 metabolism (increased hepatic T4-UDPGT activity, increased mRNA), increased clearance of radiolabelled T4, increased TSH levels and decreased T4 levels. CDER statistical analysis is pending.

Executive CAC Recommendations and Conclusions: There is a question as to whether the lymphoma reported in the mouse study was thymic lymphoma (sponsor did not specify) which occurs spontaneously in this strain. More detailed historical data for the incidence of this neoplasia is needed. The committee would also have felt more confident if 25 animals per group had been used. For the rat study, background rates of renal tubular carcinoma are needed. The committee also felt that the statistical methods used were unconventional. CDER statistical analysis is needed to complete the evaluation. A follow-up ECAC meeting will be necessary to resolve these issues once the necessary additional information is available.

/S/

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD-110
/ADeFelice, HFD-110
/EHausner, HFD-110
/DAllis, HFD-110
/ASeifried, HFD-024

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/s/

Joseph DeGeorge
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Clinical Review Cover Sheet
Original NDA Submission

NDA 21-437
Eplerenone Tablets
G.D. Searle LLC

Thomas A. Marciniak, MD
Medical Officer
Division of Cardiorenal Drug Products

Table of Contents

Clinical Review for NDA 21-437

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective the reviewer 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 of eplerenone in reducing significantly both diastolic and systolic blood pressure in patients with essential hypertension. Other studies support the efficacy of eplerenone in reducing blood pressure. 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.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The reviewer is not recommending any special Phase 4 Studies at this time

That trial will provide valuable information regarding the longer term safety profile of the drug.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Eplerenone is an aldosterone receptor competitive antagonist similar to the approved drug spironolactone. Eplerenone is formulated in tablets for oral administration. This NDA addresses the indication of the chronic treatment of hypertension.

The clinical development program for eplerenone for the hypertension indication includes 13 clinical trials and 1 open label, longer term safety and efficacy study. Two of the trials are randomized, double-blind, placebo-controlled, fixed dose, dose-ranging studies that are the pivotal studies. The other studies examine use with or compared to other drugs or specific disease subgroups or special populations. The eplerenone studies include 4908 patients, both eplerenone treated and controls. 3106 patients received at

least one dose of eplerenone. 690 were exposed for more than six months and 106 for more than one year.

B. Efficacy

Two adequate and well controlled studies, Studies 010 and 049, demonstrated that eplerenone in dosages ranging from 50 to 400 mg daily significantly reduces diastolic and systolic blood pressure in patients with essential hypertension. Study 010 was a randomized, double-blind, parallel group dose ranging trial in 409 adults with mild to moderate essential hypertension. It tested BID vs QD dosing at fixed daily dosages of 50, 100, and 400 mg for 8 weeks. It included an active control arm of spironolactone 50 mg BID as well as a placebo arm. Study 049 was also a randomized, double-blind, parallel group dose ranging trial. It randomized 390 adults with essential hypertension to fixed first morning QD dosages of 25, 50, 100, and 200 mg of eplerenone and placebo for 12 weeks. The primary endpoint for both trials was change from baseline in trough seated cuff diastolic blood pressure. Change in systolic blood pressure was a secondary endpoint.

All reductions in trough seated cuff BP were statistically significant except for diastolic blood pressure with the 25 mg QD dosage. The treatment effects were reasonable, with placebo-subtracted reductions ranging from –3.4 to –7.8 mm Hg diastolic and –5.0 to –16.6 mm Hg systolic for the dose range 50 to 400 mg daily. Both trials showed a dose-response relationship for blood pressure reduction, although the reductions were not completely consistent particularly at the higher end 200-400 mg dosages. Ambulatory blood pressure monitoring in both trials confirmed that blood pressure reductions were evident throughout the day. The data from Study 010 showed that the reductions by hour were similar with both BID and QD dosing. Treatment effect was evident within two weeks of initiating therapy and near maximal at four weeks.

Eplerenone was compared to various antihypertensives in other trials:

- Spironolactone 50 mg BID and eplerenone 400 mg daily showed comparable efficacy in essential hypertension. Spironolactone titrated 75-225 mg QD was significantly more effective than eplerenone 100-300 mg QD in controlling BP in primary aldosteronism.

- Hydrochlorothiazide 25 mg and eplerenone 200 mg produced comparable and significant reductions in SBP compared to placebo.

- Amlodipine 2.5-10 mg QD was superior to eplerenone 50-200 mg QD in reducing DBP in essential hypertension in one study. In another study amlodipine 2.5-10 mg QD was comparable to eplerenone 50-200 mg QD in reducing SBP in systolic hypertension but amlodipine was again superior in reducing DBP.

- Enalapril 10-40 mg QD was comparable to eplerenone 50-200 mg QD in reducing DBP and SBP.

- Losartan 50-100 mg QD was less effective than eplerenone 50-200 mg QD in reducing DBP both in blacks and in whites. In low renin hypertension the effects of the two drugs were comparable.

Eplerenone was added to ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers (BBs), and calcium channel blockers (CCBs) in patients not controlled on their usual dosages of one of these drugs. Eplerenone produced additional decreases in DBP and SBP with BBs and ARBs but only in SBP for ACEIs and CCBs. These results are limited by the failure to optimize use of the usual drug. The coadministrations were tolerated well.

In one study in low-renin hypertension, eplerenone was less effective in reducing blood pressure in blacks compared to whites. In a larger study, eplerenone efficacy was similar in blacks and whites, although there is evidence in this study for a slightly smaller effect in blacks. The evidence is inconclusive regarding whether eplerenone is equally effective in blacks and whites.

Eplerenone appears to produce a dose-related increase in renin and aldosterone levels. These dose effects are evident for the entire range of dosages tested, 25 through 400 mg. The 400 mg daily dosage appears slightly more effective in increasing these hormone levels than spironolactone 50 mg BID. The eplerenone increases exceed those produced by drugs with similar antihypertensive efficacy that do not act directly on the renin-angiotensin system, such as hydrochlorothiazide and amlodipine. There appears to be a differential effect of eplerenone by race and gender, with blacks and females showing reduced effect.

C. Safety

3106 patients received at least one dose of eplerenone. 690 were exposed for more than six months and 106 for more than one year. Total exposure was 1081 patient years. The recording of adverse events (AEs) and the specified laboratory monitoring was good in the clinical trials. The sponsor also performed special studies, such as drug interaction studies and pharmacokinetics in special populations, to elucidate expected safety issues.

Overall eplerenone appears to be well-tolerated. The overall rates of AEs in the placebo-controlled studies are similar for eplerenone (47.1 percent) and placebo (44.5 percent). The rates of AEs with eplerenone are higher in many of the non-placebo controlled studies, but the patient entry criteria for these latter studies selected for sicker patients, e.g., diabetics in one study and older patients in another. AE rates for eplerenone in all studies appears to be comparable to the controls, active or placebo, with the exception of

spironolactone. AE rates were substantially higher with spironolactone. However, in one study the efficacy of the dosage of spironolactone used was comparable only to the highest dosage eplerenone arm and in the other study spironolactone was more effective than eplerenone

Eplerenone has been safely coadministered with hydrochlorothiazide, ACE inhibitors, angiotensin receptor blockers, beta blockers, and calcium channel blockers. Coadministrations were tolerated well without evidence of side effects different than with the drugs used alone. Mean potassium levels were slightly greater with the coadministration of eplerenone and ARBs but clinical events of hyperkalemia remained low. With eplerenone and hydrochlorothiazide coadministration, potassium levels were intermediate between the increases seen with eplerenone and the decreases seen with hydrochlorothiazide.

The dose limiting toxicity is hyperkalemia. If hyperkalemia is defined as a maximum potassium value greater than 5.5 meq/L, then for all patients treated with eplerenone 400 mg daily the rate was about 7.8 percent. For lower dosages it was 1 percent or less. The sponsor has stated that hyperkalemia was the reason for abandoning the 400 mg dosage. For patients with mild renal insufficiency, defined as a baseline creatinine greater than 1.2 mg/dL, the rate is 37 percent with combined therapy, 27 percent with an ACE inhibitor alone, and 8 percent with eplerenone alone. However, in diabetics with microalbuminuria, the rate was 33 percent with eplerenone alone and 29 percent even with normal creatinine. The sponsor has recommended avoiding dosages greater than 100 mg in these patients and monitoring potassium levels regularly. This recommendation should minimize the risk for dangerous hyperkalemia.

Eplerenone is primarily metabolized by CYP3A4 and shows substantial increases in exposure when coadministered with potent CYP3A4 inhibitors, e.g., 540 percent increase in AUC when coadministered with ketoconazole. The sponsor has recommended that patients receiving potent CYP3A4 inhibitors should receive the lowest dose of eplerenone (25mg). This recommendation should minimize risk.

The set of toxicities that could limit usefulness long term are the sex hormone related adverse events. Eplerenone does appear to cause gynecomastia in males and it may also cause vaginal bleeding in females. The rates at which it does so appear to be lower than those with spironolactone, but the extent of the difference is unclear because spironolactone was given at more effective dosages in the two studies in which it was used and compared to eplerenone. Furthermore, gynecomastia is an AE that would be expected to manifest itself only with longer durations of exposure, i.e., six months or more. The durations of exposure in the trials, 283 patients for 180 days or more and 106 patients for more than 360 days, is not adequate to estimate precisely the incidence rates for gynecomastia with extended eplerenone exposure.

There are two incompletely addressed issues:

- Eplerenone appears to affect TSH levels. The sponsor concludes in the NDA that eplerenone does not affect TSH. The data from the three studies in which TSH levels were measured are consistent but difficult to interpret: TSH levels rose in eplerenone-treated males and in placebo or enalapril-treated females. Whether these are post-hoc, subgroup spurious results or real differences is not clear. Thyroid AE rates were higher in the open-label eplerenone group but not in the monotherapy groups. Because there is an animal model for thyroid dysfunction and because thyroid clinical effects could be delayed, it would be worthwhile to have TSH measurements and thyroid event follow-up in a larger, long term eplerenone treatment cohort.

- Whether eplerenone causes any increase in cerebrovascular or peripheral vascular thrombotic AEs is not clear. The absolute rates are low, e.g., 0.2 to 0.7 percent, but they nominally higher than in the placebo controls. The sponsor does not comment on differences in these rates possibly because the sponsor's analyses focus on rates greater than 1 percent or differences that are statistically significance. However, even a low but real increase in these rates could negate the beneficial effects of lowering blood pressure. There is a potential mechanism, increase in plasminogen activator inhibitor-1 levels, that provide a biological basis for increased thrombotic rates. Higher exposure rates are necessary to provide more precise estimates of the effects upon cerebrovascular and cardiovascular event rates.

D. Dosing

Eplerenone shows a dose-response relationship between 25 and 400 mg daily. The limitation on the use of the highest dose tested in clinical studies, 400 mg, is the risk of hyperkalemia rather than efficacy, although the precise nature of the dose-response relationship at dosages above 200 mg is not well established. Eplerenone is effective in controlling BP throughout the day with a once in the morning dosage as demonstrated by ABPM data. Eplerenone shows a substantial effect within two weeks and maximal or near maximal effect by four weeks of repeated daily dosing. The BP effects appear to be maintained at least for one year and there do not appear to be adverse withdrawal effects. Administration with food does not usually cause differences in exposure, although the administration of double-strength grapefruit juice causes 20 percent increase in eplerenone's AUC. The sponsor does not recommend dosage adjustment for grapefruit juice use. Because eplerenone will typically be titrated over a four-fold dose range and because its action is not immediate, the sponsor's conclusion is reasonable.

Eplerenone is primarily metabolized in the liver and patients with moderate hepatic impairment have a 42 percent increase in AUC. The sponsor has recommended the usual starting dose of 50 mg in these patients. This recommendation is acceptable. Eplerenone pharmacokinetics are not altered substantially with renal impairment, but the rates of one adverse event are. Hyperkalemia is more frequent with creatinine clearances of < 100 ml/min in type 2 diabetics with microalbuminuria and < 70 ml/min in other patients with essential hypertension. The sponsor has recommended avoiding doses greater than 100

mg in these patients and monitoring potassium levels regularly. This recommendation appears reasonable.

E. Special Populations

There do not appear to be any differences in BP reduction by gender or age. Eplerenone may have a differential impact upon other measures in subgroups: renin and aldosterone; liver enzymes; and sex hormones.

- Baseline renin and aldosterone levels varied by race and gender. White females had about 25 percent lower direct renin levels than white males but similar aldosterone levels. Levels in blacks were not differentiated by gender but direct renin levels were about 45 percent lower than those in white males and aldosterone levels were about 20 percent lower. Eplerenone appears to produce a dose-related increase in renin and aldosterone levels. There appears to be a differential effect of eplerenone by race and gender, with blacks and females showing reduced effect.

- Eplerenone appears to produce slight, statistically-significant, dose-related increases in ALT and GGT and has no detectable effect upon other measures of liver function. The increases in males are slightly greater than the increases in females. The GGT increase in males was picked up in the sponsor's statistical screens for AEs.

- Eplerenone appears to have a small effect upon pituitary sex hormones. In males the effects are a small decrease in FSH, a small increase in dihydrotestosterone, and possibly a small increase in LH. The effects in females are less clear because of the smaller numbers.

- Eplerenone appears to produce slight increases in TSH levels. Whether these increases are limited to or greater in males is suggested but not clearly established by the available data.

None of these effects is large. It is noteworthy that all of differences are greater effects in males. The clinical significance of them depends upon whether any clinical events result. In this NDA's database there are suggestive but not conclusive event rates.

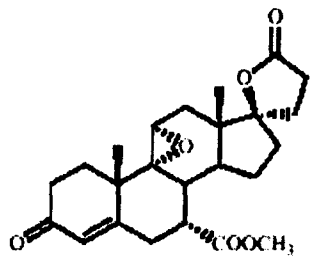
In Study 019 in low renin hypertension, blacks showed a reduced BP reduction with both eplerenone and losartan alone compared to whites. In the larger Study 020, a study that oversampled blacks and the other study with substantial black representation, there appears to be a small decrease in BP response in blacks compared to whites as well as a greater response in patients with lower baseline renin levels. Overall there is inconclusive evidence whether eplerenone is equally effective in blacks and whites.

Clinical Review

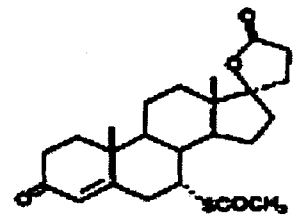
I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Eplerenone is an aldosterone receptor competitive antagonist similar to the approved drug spironolactone. The sponsor describes eplerenone as "the first agent that selectively blocks aldosterone binding at the mineralocorticoid receptor," i.e., more selective than spironolactone. Eplerenone is chemically described as [redacted] Its empirical formula is $C_{24}H_{30}O_6$ and it has a molecular weight of 414.50. The structural formulas for eplerenone and spironolactone are represented below. The presence of the 9,11-epoxide group in eplerenone reduces its progestational and antiandrogenic activity relative to spironolactone while maintaining its antimineralcorticoid effect.



Eplerenone



SPIRONOLACTONE

Figure 1: Eplerenone and Spironolactone Structures

The sponsor's proposed indication for this NDA is for the treatment of hypertension, alone or in combination with other antihypertensive agents. [redacted] The recommended starting dose for hypertension is 50 mg once daily. If blood pressure is not adequately controlled the dosage may be increased to a maximum of 200 mg daily.

The eplerenone trials have included reasonable numbers of geriatric patients, e.g., 996 patients were 65 years and older. No overall differences in safety or efficacy between these patients and younger patients were noted. Single-dose pharmacokinetics have been studied in pediatric patients but the safety and efficacy of eplerenone in pediatric patients have not been established.

The sponsor has suggested that "in Black and low-renin hypertensive patients clinical trials demonstrated enhanced effectiveness of eplerenone relative to other agents..." Eplerenone was also effective in patients with systolic hypertension.

B. State of Armamentarium for Indication(s)

Many approved agents for treating hypertension exist. Because the treatment of hypertension must typically continue lifelong and the benefits of treatment are delayed morbidity and mortality avoidance rather than immediate symptom relief, drugs for treating hypertension must have minimal side effects. The sponsor describes that "eplerenone's safety and tolerability profile was similar to other well-tolerated antihypertensive agents" and "eplerenone did not cause peripheral edema (vs. amlodipine), cough (vs. enalapril), or sex hormone-related side effects, e.g., gynecomastia (vs. spironolactone)." The sponsor also notes that eplerenone "provides the benefit of lowering BP and improving surrogate markers of CV risk." The surrogate markers improved by eplerenone in clinical studies include microalbuminuria and left ventricular hypertrophy. The sponsor reports efficacy for eplerenone in blacks, volume sensitive low-renin patients, patients with left ventricular hypertrophy, and type 2 diabetics with microalbuminuria. This review addresses the accuracy and relevance of all of these assertions.

C. Important Milestones in Product Development

The sponsor submitted IND — for eplerenone for the treatment of hypertension on October 24, 1996.

The FDA Carcinogenicity Assessment Committee subsequently approved carcinogenesis studies under the IND as follow: dosage selection for rat carcinogenesis studies in December 1996, p53 knockout mouse studies in November 1997, and dosage selection for mouse carcinogenesis studies in November 1998.

On July 17, 1998, an end-of-phase 2 meeting was held. Pertinent guidance from that meeting is the following:

- The sponsor was 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 sponsor was also advised that, when comparing their drug to an angiotensin receptor antagonist, Losartan was not the ideal choice because of its less than ideal characterization of upper dose.

- The sponsor described differentiating eplerenone from other antihypertensives by emphasizing that inhibiting aldosterone will result in various positive effects. They

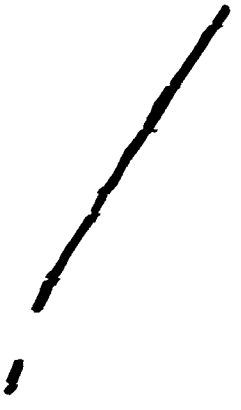
were advised that they would not be permitted implicit labeling claims for effects that were not demonstrated in adequate and well-controlled trials.

- The sponsor was advised that, in order to get a systolic hypertension indication, they would have to do a trial in a population similar to that of the SHEP trial with a design similar to the design of the SHEP trial.

- The sponsor 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. In order to make a superiority statement, they would need a placebo-controlled, dose-ranging trial that would show enhanced efficacy in the black population and that was replicated.

- Because the half-life of the drug does not support a once daily dosing regimen, they would have to confirm 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.

- The sponsor was advised that the LVH trial proposed in their package would not be useful because it was difficult to determine what claims could result from the trial.



On July 19, 2001, the Division met with the sponsor to discuss the planned NDA. The most pertinent agreements from that meeting are the following:

- The Division agreed that the primary analyses would include all randomized patients with a baseline BP measurement and at least one post-randomization BP measurement obtained before the last dose of study medication, plus one day.

- The Division noted with respect to the non-inferiority trials that it ordinarily does not pay great attention to these data. They usually do not impact the approval or non-approval process, absent a find of superiority or inferiority.

- The Division agreed that the dose-response 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.

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

- The sponsor stated an intention to seek priority review based on subgroup efficacy and effects on surrogate endpoints. The Division replied that they need to see the data supporting priority review. The Division did comment that, with regard to the surrogate endpoint albuminuria, it has not accepted it as a marker of clinical benefit. We know that drugs that lower blood pressure lower microalbuminuria but we do not have data to support it as a primary endpoint.

On December 20 and 21, 2001, the Division conducted teleconferences with the sponsor to discuss carcinogenicity issues. Please see the Section II below for a summary of these issues.

On January 11, 2002, the Division and on January 16, 2002, the Office director conducted teleconferences with the sponsor to discuss priority review. The sponsor requested priority review based on the effects of eplerenone on surrogate markers in special populations. The Division and the Office director declined to grant priority review because eplerenone appears to be another antihypertensive and an approved drug of the same class, i.e., spironolactone, exists. In further discussion on January 16 the sponsor agreed to proceed with the additional carcinogenicity studies requested by the Division, i.e., serial sectioning and blind readings of the kidneys from the standard 2-year rat study and the 2-year diet-controlled study, both sexes and all dose levels.

D. Other Relevant Information

Eplerenone has never been marketed in any foreign country.

E. Important Issues with Pharmacologically Related Agents

Eplerenone is chemically and pharmacologically similar to the approved aldosterone receptor inhibitor spironolactone (Aldactone®). The most relevant information for this review regarding spironolactone is its pharmacokinetics and side effects. Because the renin-angiotensin system also appears to be involved in fibrinolytic balance, a brief overview of effects of the renin-angiotensin system on fibrinolysis is also included below.

1. Pharmacokinetic Differences Between Eplerenone and Spironolactone

While the two drugs are pharmacologically similar, there are some relevant differences between them. Eplerenone protein binding is low (about 50 percent) while spironolactone is highly protein bound. Eplerenone is rapidly metabolized by CYP3A4 to form primary hydroxy metabolites. The metabolites are inactive at the mineralocorticoid receptor. Spironolactone is also rapidly and extensively metabolized, but its various metabolites appear to contribute to its therapeutic effects. Spironolactone metabolites include canrenone, for which the sulfur moiety is removed, and several sulfur containing metabolites. The peak serum concentrations and half-lives of the major metabolites exceed that of the native drug. All appear to have mineralocorticoid receptor blocking activity. The activity of the spironolactone metabolites must be considered in any pre-clinical comparisons of spironolactone and eplerenone.

2. Spironolactone Carcinogenicity

Spironolactone has a black box label warning for carcinogenicity. The description of the carcinogenicity studies from the label is reproduced below:

"Orally administered spironolactone has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150 and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In a 24-month study in which the same strain of rat was administered doses of about 10, 30, 100 and 150 mg spironolactone/ kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal polyps in females. A dose-related (above 20 mg/kg/day) incidence of myelocytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to spironolactone and whose primary metabolite, canrenone, is also a major product of spironolactone in man) for a period of one year. In two year studies in the rat, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular and mammary tumors. Neither spironolactone nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither spironolactone nor potassium canrenoate has been shown to be mutagenic in mammalian tests in vitro. In the presence of metabolic activation, spironolactone has been reported to be negative in some mammalian mutagenicity tests in vitro and inconclusive (but slightly positive) for mutagenicity in other mammalian tests in vitro. In the presence of metabolic activation, potassium

canrenoate has been reported to test positive for mutagenicity in some mammalian tests in vitro, inconclusive in others, and negative in still others."[1]

An IARC monograph reviewed spironolactone carcinogenicity. The IARC summary of the data is the following: "Spironolactone was tested by oral administration in two rat studies. An increased incidence of thyroid and testicular tumors was reported in one experiment but not in another experiment of longer duration with lower doses... The experimental studies, while providing limited evidence of a carcinogenic effect, were difficult to interpret because of inadequacies and inconsistencies in reporting. Epidemiological studies have not confirmed the suspicion raised by case reports that spironolactone may cause breast cancer in humans. The data are insufficient, however, to permit confident exclusion of such an effect."[2]

The epidemiological evidence regarding the carcinogenicity of spironolactone is relevant. Because spironolactone (and probably to a lesser extent eplerenone) has anti-androgenic or estrogenic effects, its potential for facilitating hormonally-related tumors such as breast cancer should be examined. One case report suggested a positive association between spironolactone use and breast cancer: Five women developed breast cancer after administration of Aldactazide® for periods of 4-24 months.[3]

Controlled epidemiological studies have not confirmed this association. Two studies that investigated an association between reserpine and breast cancer (Armstrong et al., 1974); Boston Collaborative Drug Surveillance Program, 1974) also looked at their data on spironolactone. In the BCDSP 1 of 150 breast cancer patients (0.7%) and 6 of 600 controls (1.0%) were spironolactone users. In Armstrong et al. the use was 1 of 708 in breast cancer patients (0.1%) and 2 of 1430 in age-matched controls (0.1%). The overall estimate of relative risk was 0.8 with an upper one-sided 95% confidence limit of 3.0.[4]

Another study examined spironolactone use in 481 breast cancer cases, 421 patients with benign breast lesions, and 1,268 controls from a joint national mammography screening project of the National Cancer Institute and the American Cancer Society. Previous spironolactone use was reported by 13 cases (2.7%), by 9 with negative biopsies (2.1%) and by 26 controls (2.0%). Two cases (0.4%) and 7 controls (0.6%) had used spironolactone for 5 years or more. The relative risk of breast cancer, adjusted for age, race, and screening center, was 1.4 for ever used and 0.5 for 5 or more years of therapy.[5]

One additional study used computer-stored drug-dispensing data for 143,574 outpatients to identify users of various medicinal drugs during the 4-year period beginning in July 1969. These patients were followed through 1976 for the development of cancer. 1475 persons who had received at least one prescription for spironolactone between 1969 and 1973 were followed up for cancer through 1976. Among spironolactone users, 9 cases of breast cancer were observed and 8.3 were expected. Excess cases were noted for pharyngeal cancer (2 vs. 0.1) and all cancers (84 vs. 63.1). There was an excess of 9 cases of prostatic cancer.[6]