These studies are reassuring regarding the carcinogenic potential of spironolactone both for breast cancer and for other cancers. One more relevant case series is worth noting. The Surgical Department of the Hanusch-Krankenhaus, Vienna, reviewed its 15 cases of cancer of the male breast treated between 1972 and 1988. Seven patients of the 15 (46.6%) had been treated previously with aldosterone antagonists.[7] Because of the propensity of spironolactone to cause gynecomastia in males, the association of gynecomastia with male breast cancer, and the rarity of male breast cancer, this report is of concern despite its lack of controls.

3. Spironolactone Animal Toxicity

Spironolactone animal toxicity may be compared and contrasted to that for eplerenone. A published review summarized the tissue changes in rats, dogs, and monkeys receiving spironolactone daily for up to two years. Dose levels were frequently in excess of 100 times the recommended human dose. The pituitary, adrenals, and kidneys of all animals showed no significant histologic changes. In rats that received 100 and 500 mg/kg, thyroid weight was increased in a dose-related manner and uniformly small follicles were found. The livers were enlarged. No significant changes occurred in the rat testes, but maturational arrest was found. In male rhesus monkeys, mammary acinar tissue was increased. Seminal vesicles and prostates in the rats, dogs, and monkeys were significantly reduced in weight.[8] Noteworthy compared to eplerenone is the absence of findings in the kidney.

4. Spironolactone Gynecomastia and Menstrual Irregularities

Sex hormone-related side effects of spironolactone frequently limit its use and provided major motivation for the development of eplerenone. Understanding their characteristics (frequency, dose-response, time course, etc.) is helpful for understanding eplerenone toxicity.

Spironolactone may cause these side effects by several different mechanisms. It has been shown to affect both gonadal and adrenal steroidogenesis, to elevate plasma gonadotrophin levels in children, and to act as an antiandrogen at the target tissue level.[9] It may increase the metabolic clearance rate of testosterone and increase its peripheral conversion to estradiol.[10] It may affect sex hormone metabolism through effects on the cytochrome P450 system.[11] Which of these mechanisms is responsible for the side effects is unclear. Eplerenone may have different levels of activity for any or all of these mechanisms. Increased selectivity for mineralocorticoid receptors alone does not guarantee that these side effects will be avoided.

The label for spironolactone is succinct regarding these side effects: "Gynecomastia may develop in association with the use of spironolactone; physicians should be alert to its possible onset. The development of gynecomastia appears to be related to both dosage

level and duration of therapy and is normally reversible when Aldactone is discontinued. In rare instances some breast enlargement may persist when Aldactone is discontinued... Adverse reactions... Endocrine: Gynecomastia (see Precautions), inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding."[1] Note that gynecomastia appears to be related to increasing dose and duration of treatment.

Some information on dose-response and time course to development of gynecomastia is available. Huffman et al. performed a double-blind study of spironolactone in 30 normal males for 10 months. Ten received placebo, 10 received 100 mg/day of spironolactone, and 10 received 100 mg/day initially increased to 200 mg per day after two months. Zero percent of the placebo group, 30 percent of the 100 mg/day group, and 62 percent of the 200 mg/day group developed gynecomastia.[12] Jeunemaitre et al. reported similar findings from a computerized data bank from two hypertension clinics. Among 699 men prescribed spironolactone, gynecomastia developed in 7 percent at doses of 50 mg/day or less, in 17 percent at doses between 75 and 100 mg/day, and in 52 percent at doses of 150 mg/day and higher.[13] Leizorovicz et al. compared 80 mg/day to a new aldosterone antagonist (RU 28318) in 80 patients for a year. Gynecomastia developed in 11 of the spironolactone (28 percent) and in 8 of the RU 28318 patients after 4 to 5 months of treatment.[14]

The studies referenced in the last paragraph are reasonably consistent with regard to a dose-response effect of spironolactone for gynecomastia. A plot of the dose-response is shown below.

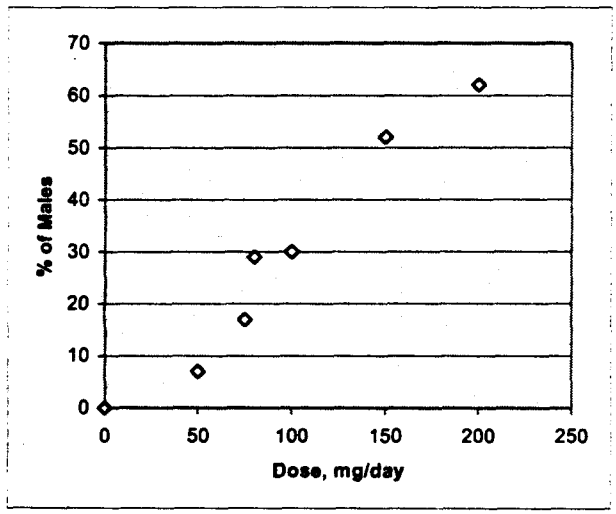


Figure 2: Reviewer's Dose-Response of Spironolactone-Induced Gynecomastia from Published Studies

The RALES trial of spironolactone in heart failure yielded rates of spironolactone-induced gynecomastia consistent with those shown in Figure 2.[15] In RALES 822 (603

male) patients received 25-50 mg of spironolactone daily (mean 26 mg) for a mean follow-up period of 24 months. Nine percent of the treated patients developed gynecomastia vs. 1 percent in the placebo group. While arguably higher than the rates in Figure 2, the RALES rate may be considered consistent because of the longer duration of treatment (24 months) and possibly because of sensitive ascertainment (1 percent rate in the placebo group.)

Jeunemaitre et al. observed that the duration of treatment prior to development of gynecomastia was variable, ranging from 2 to 100 months. It was shorter for doses of 150 mg/day or more (9 months) than for doses of 50 mg/day or less (27 months).[13] Leizorovicz et al. provide data on the development of gynecomastia at 80 mg/day. Their data on the cumulative incidence over time are plotted below.[14]

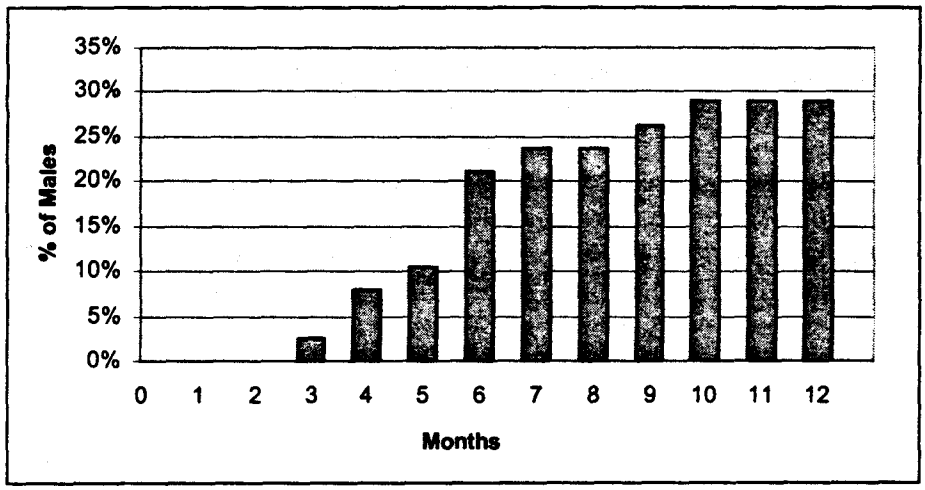


Figure 3: Reviewer's Time to Gynecomastia at Spironolactone 80 mg/day from Leizorovicz et al.

5. Spironolactone and Hyperkalemia

Besides gynecomastia hyperkalemia is the other major dose-limiting toxicity of spironolactone. Worrisome hyperkalemia with spironolactone is usually associated with higher doses, reduced renal function, or the use of potassium supplements or potassium-sparing drugs. In the RALES trial median serum potassium increased by 0.3 mmol/l. Serious hyperkalemia occurred in 10 patients in the placebo group (1%) and 14 patients in the spironolactone group (2%).[15] Schepkens et al. recently reported 25 cases of life-threatening hyperkalemia associated with combined ACE inhibitor and spironolactone therapy. On admission the mean serum potassium was 7.7 mmol/l and the mean serum creatinine was 3.8 mg/dl. The mean daily dosage of spironolactone was 57 mg. They concluded that hyperkalemia with spironolactone was associated with renal insufficiency, diabetes, older age, worsening heart failure, a risk for dehydration, and combination with other medications causing hyperkalemia.[16] Butler et al. very recently noted that

spironolactone at a dosage of 50 mg daily causes hyperkalemia (potassium > 5.0 mmol/l) in elderly patients with heart failure and recommended close monitoring and halving the dose if hyperkalemia ensues.[17]

5. Renin-Angiotensin System and Fibrinolytic Balance

The renin-angiotensin system appears to play a role in fibrinolytic balance.[18] Fibrinolysis is accomplished through the plasminogen activator system. Plasminogen is acted upon by one of two plasminogen activators (tissue plasminogen activator, or t-PA, the predominant plasminogen activator in blood, and urokinase-type plasminogen activator, or u-PA) to produce the proteolytic enzyme plasmin. Plasmin breaks down fibrin. The activity of t-PA is controlled by plasminogen activator inhibitor-1 (PAI-1), which binds to t-PA and inactivates it. Both angiotensin II and bradykinin cause the release of PAI-1.

Observational studies suggest that high PAI-1 levels are associated with cardiovascular disease. In various studies young myocardial infarction (MI) survivors had higher levels than matched controls and high levels have been associated with reinfarction, coronary artery disease progression, and first occurrence of an MI. Elevated levels of t-PA have also been associated with cardiovascular risk. However, total levels may reflect bound PAI-1/t-PA complexes, so t-PA activity may be a preferable measure of the contribution of t-PA to risk. The relationship between PAI-1 and cardiovascular risk is not clear. For example, post-menopausal women have elevated levels of PAI-1 and hormone replacement therapy reduces them. The recent evidence that hormone replacement therapy does not reduce thrombotic events does not support a simple relationship between PAI-1 and cardiovascular risk.

Drugs may affect PAI-1 levels. In one study normotensive subjects on a low-salt diet (to activate the renin-angiotensin system) showed a diurnal variation in PAI-1 and t-PA levels. Quinapril reduced mean 24-hour PAI-1 levels but did not change t-PA levels. Losartan in a similar study did not affect PAI-1 levels, but in a study of patients with severe heart failure losartan decreased PAI-1 and increased t-PA six hours after a single dose while enalapril produced insignificant small increases in both. In another study in patients with a MI, ramipril reduced PAI-1 by 44 percent after 14 days. Spironolactone 100 mg QD and hydrochlorothiazide (HCTZ) 25 mg QD were studied in nine male hypertensive subjects for two weeks.[19] In this study spironolactone but not HCTZ reduced SBP while both increased angiotensin II and aldosterone (although spironolactone more than HCTZ for aldosterone). HCTZ increased PAI-1 and did not affect t-PA while spironolactone increased t-PA and left PAI-1 unchanged.

All of these studies confirm that the renin-angiotensin system plays a role in fibrinolytic balance but they do not delineate how changes in fibrinolytic system factors mediated by drugs affect cardiovascular risk. The sponsor elected to measure PAI-1 and t-PA in five of the NDA clinical studies. This section provides a background for interpreting the results of those measurements.

F. Abbreviations Used in this Review

The following are abbreviations, other than standard measurement units, used in this review:

ABPM	ambulatory blood pressure monitoring
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
Alk phos	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the curve
BB	beta blocker
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
CAC	Carcinogenicity Assessment Committee (FDA)
CCB	calcium channel blocker
CL	clearance
C_{max}	maximum concentration
Coadmin	coadministration
CPN	chronic progressive nephropathy (in rats)
CYP	cytochrome P-450
DBP	diastolic blood pressure
DSI	Division of Scientific Investigations (FDA)
E	eplerenone
ECG	electrocardiogram
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GGT	gamma glutamyl transpeptidase
HCTZ	hydrochlorothiazide
IARC	International Agency for Research on Cancer
IND	Investigational New Drug
IRB	Investigational Review Board
LH	luteinizing hormone
LOCF	last observation carried forward
LVH	left ventricular hypertrophy
LVM	left ventricular mass
MI	myocardial infarction
Mono	monotherapy
NDA	New Drug Application

NOAEL	no adverse effect level
PAI-1	plasminogen activator inhibitor-1
PD	pharmacodynamic
PEY	patient exposure years
PK	pharmacokinetic
QD	once daily
QTc	QT interval duration corrected for heart rate
RAAS	renin-angiotensin-aldosterone system
RD	risk difference
SAE	serious adverse event
SAS®	Statistical Analysis System
SBP	systolic blood pressure
se	seated
SL	spironolactone
$T_{1/2}$	half-life
T_{max}	Time to maximum concentration
t-PA	tissue plasminogen activator
TSH	thyroid stimulating hormone
UACR	urinary albumin:creatinine ratio

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

For a comprehensive review of the pre-clinical studies, see the pharmacologist's review of the NDA. This brief section highlights the pre-clinical findings most relevant to the safety and efficacy of eplerenone in humans and to the proposed labeling statements.

A. Sponsor's Summary of Animal Toxicity

The sponsor's summary of the relevant animal toxicity studies is the following:

"The nonclinical safety assessment program showed eplerenone was not overtly toxic, i.e., it did not cause clinical signs of illness or death in animals, except at highly exaggerated dosages and systemic exposure multiples in the dog and the mouse. The principal long-term adverse effects in animals included acceleration of chronic progressive nephropathy (CPN), a rat-specific chronic renal disease, and reduced prostate size in dogs, which was fully reversible. None of these changes is considered a significant hazard for humans, and they occur only at multiples of the human doses and the associated systemic exposure levels.

"Some effects of eplerenone in animals appear to be associated with exaggerated aldosterone receptor antagonism. These effects, which include serum and urinary electrolyte changes (e.g., increased urine sodium and potassium ratio) and increased serum aldosterone in rats and dogs, are reversible upon discontinuation of treatment. Rats and dogs also had histological evidence of hypertrophy of the adrenal zona glomerulosa, site of aldosterone synthesis and secretion. Serum cortisol increased in dogs administered 25 or 100 mg/kg/day and equivocally at 5 mg/kg/day. These changes were reversible. Spironolactone increased cortisol to about the same degree as eplerenone when both were dosed at 5 mg/kg/day.

"Rats and mice had increased liver weights as the result of metabolic enzyme induction. Systemic exposure to eplerenone tended to decrease over time in these species. Rats frequently had elevations of serum cholesterol, triglycerides and total protein, which were reversible and were considered to be secondary to hepatic enzyme induction and enlargement

"CPN incidence was mildly increased in rats administered 500 mg/kg/day for 13-weeks or six-months, or in females administered 250 mg/kg/day for 1-year. The no observed adverse effect level (NOAEL) for this effect was 100 mg/kg/day for female rats and 200 mg/kg/day for male rats. The exposure multiple at the NOAEL is approximately four times the human therapeutic AUC. It is characterized by progressive degenerative changes in nephrons with early loss of protein in the urine. CPN is a rat disease that does

not have a direct human counterpart. The increased incidence is not considered to represent an issue for human safety.

"In the dog, decreases of prostate weight were observed at dosages of 15 mg/kg/day and higher, giving exposure multiples at least 5x that at the human dose of 100 mg. The NOAEL for the prostate effect was 5 mg/kg/day, which gave a 2x exposure multiple. However, a spironolactone comparator group receiving 5 mg/kg/day in a 13-week study had a greater decrease in prostate weight than a group receiving 25 mg/kg/day of eplerenone. The eplerenone-related prostate effect was fully reversible by the end of a three-month recovery period, even after a full year of dosing at 100 mg/kg/day. The mechanism of the prostate shrinkage is apparently related to blockage of androgen receptors at concentrations above those needed to block aldosterone receptors. In vitro studies demonstrated that eplerenone, at high concentrations, can inhibit binding of dihydrotestosterone to dog prostatic androgen receptors; spironolactone, however, was 1000-fold more potent for this activity. In another dog study, no changes in sexual behavior, semen quality, sperm production, or testicular weight or histology were observed in response to eplerenone, even at doses that caused prostate shrinkage.

"Eplerenone was not genotoxic in an extensive battery of tests. No eplerenone-related tumors occurred in a six-month carcinogenicity study in p53 heterozygous knock-out mice. In a two-year carcinogenesis study in rats there were no eplerenone-related malignancies. There were, however, increased incidences of benign thyroid follicular cell tumors. This was secondary to induction of the hepatic enzyme UDPGT, which causes increased biliary excretion of thyroid hormones and feedback TSH stimulation of the thyroid gland. This mechanism of thyroid tumor formation occurs in rats with several marketed drugs and is considered irrelevant to humans. Spironolactone, in a two-year rat study, was associated with malignant and benign thyroid tumors as well as tumors of the liver, testis and uterus.

"There was no evidence of eplerenone-related teratogenicity in rats up to the ICH guideline maximum dose of 1000 mg/kg/day or in rabbits at 300 mg/kg/day, a dosage that caused maternal toxicity. Eplerenone caused no adverse effects on fertility in female rats at dosages up to 1000 mg/kg/day (AUC 32 times that of the maximum human therapeutic dose). Fertility in male rats was slightly decreased (reduced implantation sites when bred to untreated females) at 1000 mg/kg/day (AUC 17 times that of the maximum human therapeutic dose). This effect was apparently related to decreased size of the seminal vesicles and resultant smaller copulatory plugs. Since humans do not form copulatory plugs, this effect is considered irrelevant for human fertility. In a pre- and postnatal development study in rats, eplerenone caused a slight reduction in birth weights of pups from dams dosed with 1000 mg/kg/day, but there were no adverse postnatal effects. In rats, small changes in some clinical chemistry, hematology, and organ-weight measurements occurred consistently across studies at dosages of 250 and 500 mg/kg/day and sporadically at lower dosages. These changes were regarded as small and toxicologically insignificant, and they occurred at systemic exposure levels of free eplerenone that were at least four times the human therapeutic AUC(0-24 hours)."

B. Carcinogenicity

Eplerenone 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. However, in a standard 2-year rat study the incidence of 2 renal tumors in the high dose females versus 0 incidence in the control females prompted the FDA Executive Carcinogenicity Advisory Committee (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. After evaluation of the additional information submitted by the sponsor the CAC concluded that the renal neoplasia in high dose female rats was not a biologically significant finding. Please see the FDA pharmacologist's review for a detailed description of the findings in the original 2-year rat study, the requested additional studies, and the CAC's evaluation.

C. Mineralocorticoid Receptor Selectivity

The sponsor proposes including the following table regarding mineralocorticoid receptor selectivity in the labeling:

Receptor (standard)	Eplerenone
Mineralocorticoid (aldosterone)	0.005 (n 7)
Androgen (methyltrienolone)	0.0000076 (n 6)
Glucocorticoid (dexamethasone)	0.00018 (n 4)
Progesterone (progesterone)	< 0.00005* (n 5)

Affinities expressed as a fraction of the binding affinity of the standard ligand at each receptor. Binding affinity of the standard ligand is set at 1. *Due to poor solubility of eplerenone at high concentrations in the assay conditions, this value is difficult to estimate.

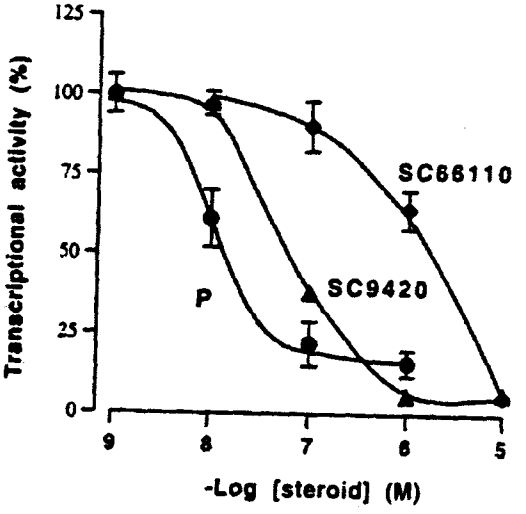
(Table 1 from Proposed Labeling)

Figure 4: Sponsor's Relative Binding Affinities of Eplerenone for Steroid Receptors In Vitro

The numbers in the above figure are taken from the publication de Gasparo M, Joss U, Ramjoue HP, Whitebread SE, Haenni H, Schenkel L et al. Three new epoxy-spironolactone derivatives: characterization in vivo and in vitro. J Pharmacol Exp Ther 1987; 240:650-656. The steroid receptors used were rat receptors.

The activity of eplerenone at human steroid receptors was also measured in vitro using recombinant human steroid receptors. The sponsor's summary of the human receptor studies is the following: "Eplerenone inhibited human mineralocorticoid receptor (MR) transcriptional activation by aldosterone in a concentration-dependent manner with a calculated IC50 of 291 nM (29). In an independent assay, eplerenone and spironolactone both inhibited aldosterone-induced activation of the human mineralocorticoid receptor and spironolactone was approximately 20-fold more potent than eplerenone in blocking the aldosterone response. However, the selectivity of eplerenone was significantly greater than spironolactone at androgen, progesterone and glucocorticoid receptors. Whereas spironolactone at 10^{-5} M inhibited 65% of the maximal activation of human androgen receptor by the agonist methyltrienolone, eplerenone inhibited only 5% of the response at the same concentration (10^{-5} M). Similarly, using human recombinant progesterone receptor, eplerenone at 10^{-5} M inhibited 5% of progesterone receptor activation compared to the 50% inhibition observed with spironolactone at the same concentration. At recombinant human glucocorticoid receptors, eplerenone did not inhibit the maximal dexamethasone-induced activation of the receptor at 10^{-5} M compared to a 25% inhibitory response for spironolactone (30). Using human steroid receptors these data confirm earlier studies using steroid receptor preparations from animal tissues demonstrating that eplerenone is a significantly more selective mineralocorticoid receptor antagonist compared to spironolactone."

Document number BRD00D2049, "EPLERENONE: A SELECTIVE MINERALO-CORTICOID RECEPTOR ANTAGONIST," from the NDA includes the following graph showing the inhibition of human mineralocorticoid receptor activity by eplerenone and spironolactone:



SC66110 = eplerenone; SC9420 = spironolactone (Figure 3)

Figure 5: Sponsor's Effect of Increasing Concentrations of Steroids on the Aldosterone-induced Human Mineralocorticoid Receptor Activity

The following figure shows the data from this study regarding progesterone receptor activity inhibition.

Steroids	Activity (AU)	Mean ±SEM	Activity (%)
Progesterone (10^{-8}M)	308 348 278	311 ± 20	100 ± 6
Spironolactone (10^{-5}M)	151 165 119	145 ± 14	46.6 ± 4.5
Eplerenone (10^{-5}M)	15.3 22.1 11.8	16.4 ± 3.0	5.3 ± 1.0
Progesterone (10^{-8}M) + Spironolactone (10^{-5}M)	215 139 138	164 ± 25	52.7 ± 8.0
Progesterone (10^{-8}M) + Eplerenone (10^{-5}M)	302 226 220	249 ± 26	80.1 ± 8.4
Progesterone (10^{-8}M) + RU486 (10^{-5}M)	55 18 25	32.7 ± 11.3	10.5 ± 3.6

(Table 1.4)

Figure 6: Sponsor's Inhibition of Human Progesterone Receptor Activity

Note that eplerenone at 10^{-5} M appears to inhibit about 20 percent of progesterone receptor activation compared to the 47 percent inhibition observed with spironolactone at the same concentration.

The following figure shows the data from this study regarding androgen receptor activity inhibition.

APPEARS THIS WAY
ON ORIGINAL

Steroids	Activity (AU)	Mean ±SEM	Activity (%)
R1881 (10^{-8}M)	699 663 698	687 ± 12	100 ±2
Spironolactone (10^{-5}M)	273 218 218	236 ± 18.3	34.3 ± 2.6
Eplerenone (10^{-5}M)	51 26 33	36.7 ± 7.4	5.3 ± 1.1
R1881 (10^{-8}M) + Spironolactone (10^{-5}M)	270 194 261	242 ± 24	35.1 ± 3.6
R1881 (10^{-8}M) + Eplerenone (10^{-5}M)	687 575 580	614 ± 36	89.4 ± 5.2
R1881 (10^{-8}M) + RU486 (10^{-5}M)	241 300 327	289 ± 25	42.0 ± 3.6

R1881 = methyltrienolone (Table 1.5)

Figure 7: Sponsor's Inhibition of Human Androgen Receptor Activity

Note that eplerenone at 10^{-5} M appears to inhibit about 10 percent of progesterone receptor activation compared to the 65 percent inhibition observed with spironolactone at the same concentration.

Reviewer's comment: The human receptor inhibition study is not convincing that the relative potencies of eplerenone and spironolactone are dramatically different for inhibiting the various steroid receptors. If the dose-response curves for receptor inhibition are similar, then the data above are consistent with similar relative potencies of the two drugs for all receptors. Note also that spironolactone metabolites such as canrenone are active so that to be convincing any in vitro comparisons would have to account for their activities as well as those of the parent drug.

The table on relative binding affinities for rat steroid receptors may be misleading for human use and does not belong in the labeling. The important observations for human use are not the in vitro receptor binding or activity inhibition but the clinical effects, e.g., gynecomastia, menstrual irregularities, that the drugs produce. These are summarized elsewhere in the NDA and in this review and will be included in the label.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

For a complete review, see the biopharmaceutics review of the NDA. The material presented here is reproduced from the sponsor's summary and is included here as background to the review of the clinical data contained in the NDA. No study reports or primary data have been reviewed by the medical officer.

1. Basic Pharmacokinetics

The sponsor's summary of eplerenone metabolites is the following: "Eplerenone (other names include SC-66110, CGP 30 083, epoxymexrenone) undergoes cytochrome P450-catalyzed metabolism to form a primary hydroxy metabolite 6βOH (SC-71597), which is further catalyzed by CYP3A. Other metabolic steps include biological conversion of eplerenone to the lactone ring-opened form (SC-70303 free acid), hydroxylation at the 21-position and reduction of the 3-ketone to 3α-OH eplerenone. In all, nine eplerenone metabolites have been identified in human urine or feces. The 6β-OH, 6β-21-OH and 21-OH metabolites were the major metabolites of eplerenone recovered in the urine, representing approximately 28%, 13%, and 5% of the dose, respectively. (12) The remaining metabolites identified represent less than 10% of the total of the dose. The conversion of SC-66110 to SC-70303 free acid is pH-mediated (Figure 4.a). In solution, these analytes exist in equilibrium, while in plasma, the expression of SC-70303 free acid is 7% to 12% that of SC-66110."

"After oral administration, all species (including human) were systemically exposed to the lactone ring-opened form of eplerenone (SC-70303 free acid). Due to low affinity for the mineralocorticoid receptor, SC-70303 free acid does not contribute markedly, nor do the major human metabolites of eplerenone, to the in vivo anti-mineralocorticoid activity. The IC50 values for binding to the rat colon mineralocorticoid receptor are 308, 1565, 2554 nM for eplerenone, 6β-OH eplerenone and SC-70303 free acid, respectively. The IC50 values for 21-OH eplerenone and 6β, 21-OH eplerenone were greater than 10,000 nM." Document Number BRD01D2119 in the NDA, "HUMAN MINERALOCORTICOID RECEPTOR BINDING OF TWO EPLERENONE (SC-66110) METABOLITES, THE OPEN LACTONE RING FORM OF EPLERENONE (SC-70303) AND 6β-OH EPLERENONE (SC-71597)" has the following summary of the activity of the metabolites: "For the human mineralocorticoid receptor, percent inhibition of human MR transcriptional activity was determined for each metabolite with calculated IC50 values of 8.2 μM for the open lactone ring form of eplerenone and 17 μM for 6β-OH eplerenone (Table 2), as compared to 291 nM for eplerenone."

The sponsor's summary of eplerenone pharmacokinetics is the following:

"Eplerenone is a low-solubility, high-permeability drug that exhibits excellent oral bioavailability (about 67%) and minimal first-pass effect. The absolute bioavailability of eplerenone is not known because there is no intravenous formulation. Following oral dosing in young healthy adults, its mean (SD) plasma clearance was 9.6 (4.0) L/hr, the steady-state volume of distribution was 49 (7.3) L, and the terminal half-life was 4.3 (1.3) hours. Eplerenone was not highly bound (only about 50%) to human plasma proteins and this protein binding was concentration-independent within the expected therapeutic range of total plasma concentrations. Eplerenone did not selectively partition into erythrocytes, with the average ratio of plasma/whole blood concentrations of eplerenone being relatively constant with time or concentration.

"Eplerenone is extensively metabolized in humans and less than 10% of the radio-labeled dose was recovered as unchanged total eplerenone in urine plus feces. Elimination of eplerenone involved phase I metabolism, including hydroxylation of the methyl group to form the several pharmacologically-inactive metabolites. In vitro studies indicated that formation of SC-71597 was predominantly mediated by CYP3A4. Plasma exposure of the inactive metabolite SC-71597 was constant at about 32% of the concentration of eplerenone in healthy adult subjects. Eplerenone also underwent extensive metabolism to form other pharmacologically inactive metabolites.

"Dose proportionality in AUC of eplerenone was demonstrated for the capsule formulation after single-doses between 10 mg and 100 mg, and for the proposed commercial formulations of 25 mg, 50 mg, and 100 mg tablets. Administration of eplerenone tablets with food delayed T_{max}, but had little or no effect on the extent or rate of eplerenone absorption. Eplerenone coadministration with an aluminum-magnesium hydroxide antacid resulted in slightly earlier T_{max}, but had little or no effect on the extent or rate of eplerenone absorption. Eplerenone coadministration with double-strength grapefruit juice resulted in 19% and 29% increases in AUC and C_{max}, respectively, but these changes are not considered clinically significant. Plasma concentrations of eplerenone were at or near steady state within four days of repeated QD doses of eplerenone. In a 14-day multiple-dose study, there were no significant changes in steady-state eplerenone plasma concentrations after seven days of QD dosing under fasted conditions, indicating no auto-induction or inhibition of eplerenone."

2. Pharmacokinetics in Special Populations

The sponsor's summary of eplerenone pharmacokinetics in special populations is the following:

"Healthy elderly subjects receiving eplerenone 100 mg QD showed a reduction in apparent plasma clearance of eplerenone compared to healthy young subjects, resulting in a 45% (female) to 46% (male) higher plasma exposure (AUC_{0-24}) of eplerenone. Steady-state plasma exposure of eplerenone, adjusted for body weight, was approximately 3%

higher (3% reduction in average plasma CL/F) in elderly females compared to elderly males. The higher eplerenone plasma exposure in elderly women and elderly men was attributed to age. The magnitude of the differences in eplerenone plasma clearance between males and females, and between the young and elderly, was generally not considered large enough to require dose adjustment due to the wide therapeutic index of eplerenone.

"Steady-state peak concentration (C_{max}) and total (AUC_{0-24}) plasma exposure of eplerenone after multiple 400 mg oral doses of eplerenone were 4% and 42% higher, respectively, in patients with moderate hepatic impairment (Child-Pugh B) compared to age- and gender-matched subjects with normal hepatic function. The magnitude of the differences in eplerenone plasma clearance between patients with moderate hepatic impairment and subjects with normal hepatic function was not large enough to require dose adjustment. Patients with severe hepatic dysfunction were not studied.

"In patients with severe renal dysfunction ($CL_{cr} \leq 25.5$ mL/min/1.73 m^2) and those with end-stage renal disease treated with hemodialysis, average steady-state plasma CL/F of eplerenone was reduced by only 27% (38% increase in eplerenone AUC_{0-24}, and increased 35% (27% decrease in eplerenone AUC_{0-24}), respectively, compared to age-related subjects with normal renal function. The average ratio of eplerenone AUC_{0-24} to SC-71597 AUC_{0-24} after multiple 100 mg oral doses of eplerenone in patients with severe renal impairment was 1.6, and only slightly lower than that observed in matched healthy subjects, suggesting that conversion of eplerenone to SC-71597 is not altered in patients with renal impairment. These findings further supported the view that renal excretion of eplerenone is not important in its overall elimination from the body.

"Hemodialysis removed only about 10% of the administered eplerenone dose from the systemic circulation of eight end stage renal disease patients; therefore, on a pharmacokinetic basis alone, no dosage adjustment would be required for the hemodialysis procedure."

3. Drug-drug Interactions

The sponsor's summary of eplerenone drug-drug interactions is the following:

"In vitro studies demonstrated that CYP3A4 is the most likely isozyme responsible for the metabolism of eplerenone. The hydroxylated metabolite is formed first and is considered to be the rate-controlling step in the overall metabolic elimination of eplerenone.

"Coadministration of eplerenone 100 mg QD with digoxin 200 g QD, simvastatin 40 mg QD, midazolam 10 mg QD, cisapride 20 mg QD, cyclosporine 400 mg QD, oral contraceptives (Ortho-Novum 1/35 ® 28-day Regimen), and St. John's Wort 300 mg TID resulted in minor changes in mean plasma exposure and/or mean plasma clearance in

or both of the coadministered compounds. None of these changes in pharmacokinetic parameters was considered to be of a sufficient magnitude to warrant changes to the standard dosing regimens.

"The short-term coadministration of warfarin 1 to 15 mg QD and eplerenone 100 mg QD to healthy subjects did not significantly alter the pharmacokinetics of either compound, nor did coadministration have a clinically important effect on the anticoagulant activity of warfarin.

"Eplerenone (100 mg QD for seven days) coadministered with glyburide (5 mg QD or 10 mg BID for seven days) did not produce clinically important changes in the pharmacokinetics of glyburide in patients with Type 2 diabetes mellitus. Small, but statistically significant, eplerenone-related changes were found in the pharmacodynamic effects (blood glucose and insulin) of glyburide despite the fact that plasma concentrations of glyburide were not significantly different between placebo and eplerenone treatments. The small decreases in eplerenone-related blood glucose and insulin concentrations were not considered to be of a large enough magnitude to be clinically important.

"Coadministration of single 100 mg oral doses of eplerenone with ketoconazole (200 mg BID for seven days) or fluconazole (200 mg QD for seven days) significantly inhibited the apparent plasma clearance of eplerenone, resulting in statistically significant increases (441% and 123%, respectively) in total plasma exposure ($AUC_{0\text{-}inf}$) of eplerenone. These findings showed the importance of CYP3A4 in the metabolic clearance of eplerenone in humans.

"Coadministration of erythromycin with eplerenone 100 mg QD for seven days significantly increased total plasma exposure of eplerenone; eplerenone coadministration with erythromycin did not have any clinically significant changes on erythromycin total plasma exposure.

"Coadministration of verapamil with eplerenone 100 mg QD for seven days significantly increased total and maximum plasma exposure of eplerenone; eplerenone coadministration with verapamil did not have any clinically significant changes on verapamil plasma exposure.

"Coadministration of saquinavir with eplerenone 100 mg QD for seven days significantly increased total plasma exposure of eplerenone; eplerenone coadministration with saquinavir did not show any clinically significant changes in saquinavir.

"Because they may inhibit the metabolism of eplerenone, patients receiving CYP3A4 inhibitors such as fluconazole, erythromycin, verapamil and saquinavir, should receive the 50 mg dose of eplerenone.

"When eplerenone is coadministered with ketoconazole, or other potent CYP3A4 inhibitors, patients should receive the 25 mg dose of eplerenone."

B. Pharmacodynamics

For a complete review, see the biopharmaceutics review of the NDA. The material presented here is reproduced from the sponsor's summary and is included here as background to the review of the clinical data contained in the NDA. No study reports or primary data have been reviewed by the medical officer.

The following is the sponsor's summary of pharmacodynamic effects of eplerenone other than effects upon blood pressure and electrocardiographic parameters:

"Urinary sodium and potassium excretion are influenced by the presence of aldosterone. As a measure of the aldosterone receptor antagonism effects of eplerenone, clinical trials evaluated the urinary log10 (Na + /K +) ratio, a measurement of mineralocorticoid agonist activity in healthy subjects with fludrocortisone-induced changes in urinary sodium and potassium excretion.

"Following single oral 100 mg, 200 mg, 400 mg, or 600 mg doses of a non-optimized formulation of eplerenone (CGP 30 083) in the first study (Ciba-Geigy 115/86 [72]), the urinary log10 (Na + /K +) ratio data indicated a dose-dependent eplerenone aldosterone-antagonist effect. Eplerenone appeared to be maximally effective at 100 mg as measured by the antagonism of aldosterone since there was no statistically significant difference between the 100 mg and 200 mg doses, while spironolactone reached its maximal effect at 200 mg. The maximal effect of eplerenone and spironolactone were comparable.

"In Study 001, a single rising dose tolerance study, eplerenone increased urinary log10 (Na + /K +) in a dose-related manner between doses of 50 mg to 1000 mg. In Study 004, eplerenone significantly increased urinary log10 (Na + /K +) at doses of 100 mg to 1000 mg following single-dose administration. There was no sustained increase in log10 (Na + /K +) values, however, following multiple-dose administration of either eplerenone or spironolactone. Eplerenone showed potent antialdosterone activity following the fludrocortisone challenge in Study 004. In both Study 001 and Study 004, the potencies of eplerenone and spironolactone were not significantly different.

"Increased plasma renin (total and active) and serum aldosterone following aldosterone receptor antagonism is well recognized and reflects inhibition of the RAAS feedback loop. The increased activity of RAAS is an expected result of aldosterone receptor antagonism by eplerenone. Eplerenone at doses as low as 25 mg QD were pharmacologically active as evidenced by the mean percent increases from Baseline in plasma renin (total and active) and serum aldosterone across clinical trials. The results from the 11-day multiple rising dose tolerance study (Study 004) in healthy subjects indicated a significant dose-related response in mean plasma renin (active and total) and

serum aldosterone levels with eplerenone at doses ranging from 100 mg to 1000 mg. In the dose-ranging Study 010, eplerenone increased the activity of the RAAS obtained 24 hours after the last dose of QD administration, suggesting a greater than 24-hour biological action of eplerenone in blocking the effect of aldosterone.

"Eplerenone increased RAAS hormone activity consistently across clinical studies. This pharmacological activity was observed in doses ranging from 25 mg QD to 200 mg QD. The eplerenone-related increases in active and total plasma renin and serum aldosterone were consistent with blockade of the aldosterone receptor and compensatory feedback activation of the RAAS. At doses compared in Study 018, spironolactone significantly increased RAAS compared to eplerenone. Results from other comparator-controlled studies varied in the relative activation of RAAS compared to eplerenone. This variation may be due to differences in doses and in study design, including length of treatment, and mechanism of action of the comparator agent. Coadministration of a calcium channel-blocking or beta-blocking agent had no apparent inhibitory effect on the eplerenone-related RAAS activity. Of note was the greater magnitude (approximately three-fold) of increased RAAS activity among black subjects compared to white subjects (Study 020).

"As microalbuminuria has been shown to be associated with high BP, a higher risk for cardiovascular dysfunction LVH, MI, stroke, peripheral vascular disease, retinopathy, and renal disease, (78-82) reductions in urinary albumin excretion have clear clinical benefit. Eplerenone administration consistently reduced urinary albumin, as measured by UACR, across clinical studies. In addition to demonstrating the UACR-lowering effects of eplerenone in hypertensive patients (Studies 016 and 022), the clinical development program included studies with patients with co-morbidities (Studies 017 and 021). Change from Baseline to end of treatment in UACR was used to determine the effect of eplerenone on microalbuminuria and was a secondary outcome measures in Studies 016, 017, and 020. In each study, eplerenone administration resulted in significant reductions in UACR adjusted mean percent change from Baseline to Final Visit as compared to a placebo control (Study 020) and similar reductions in compared to losartan (Study 020) and to enalapril (Study 017). This reducing effect observed with eplerenone was significantly enhanced when eplerenone was coadministered with enalapril in Study 017. Taken together, these data suggest a nephroprotective effect of eplerenone comparable to that seen with ACE inhibitors and A-II antagonists.

"The effects of aldosterone are far reaching and include alterations in aortic compliance, in LVM in LVH, fibrinolytic activity, and collagen activity when aldosterone levels are elevated. The clinical development program of eplerenone included, as secondary measures, evaluation of aortic compliance (Study 017, 022) changes in LVM (Study 017, a primary endpoint), and monitoring of fibrinolytic (Studies 017, 021, and 026) and collagen activity (Studies 016, 017, 021, 022). When compared to enalapril, eplerenone resulted similar mean reductions in LVM at the end of a nine-month treatment period. When enalapril was combined with eplerenone, the mean reduction in LVM was significantly greater than that observed with eplerenone alone.

"Analyses of arterial compliance were based on the recorded PWV as measured by the ——— device. The change from Baseline in carotid-femoral and carotid-radial PWV was assessed at Week 14 and Week 24. Both drugs tested, eplerenone and amlodipine, resulted in significant, but similar, mean reductions in PWV.

"Overall, eplerenone had no significant clinical effect on fibrinolytic or collagen activity when compared to enalapril (Studies 017 and 021) or amlodipine (Studies 021 and 026). However, data from Study 017 suggests an enhanced effect of increased collagen marker activity with an eplerenone/enalapril combination therapy."

IV. Description of Clinical Data and Sources

A. Overall Data

The NDA is an electronic submission, although the first three summary volumes were also provided in paper versions. The clinical data sections of the NDA (2. Labeling, 3. Summary, 8. Clinical Data, 11. Case Report Tabulations, and 12. Case Report Forms) were the primary information sources used for this review. These files describe the sponsor's experience with eplerenone. The Case Report Tabulations were provided as SAS transfer data sets that were used to confirm the sponsor's statistical analyses and to perform other reviewer-defined analyses relevant both to efficacy and to safety. A literature search focusing on background material regarding spironolactone was also used as described under Literature Review below.

The NDA submissions used for this review are summarized in the table below:

Table 1: Reviewer's NDA Submissions Used in Review

Submission Date	Description
11/28/01	Original NDA
01/04/02	Replacement for illegible tables
01/15/02	Replacement for pharmtox section
04/05/02	120-Day Safety Update
04/30/02	Responses to questions

B. Tables Listing the Clinical Trials

The sponsor conducted fourteen clinical studies to demonstrate the antihypertensive efficacy of eplerenone. Two were placebo-controlled, fixed-dose, monotherapy studies (010 and 049). These two studies are the pivotal studies for this NDA. The eleven randomized, blinded studies focusing on the blood pressure effects of eplerenone are listed in the figure below. Two additional controlled studies focusing on non-BP endpoints are listed in the second figure and the uncontrolled, open-label follow-on study is listed in the third figure below.

Study grouping	Study Number	Eplerenone Dose (a)	Main entry criteria/ Primary Endpoint†	Pbo control	Active control (doses)	Co-administration	Dosing protocol (b)	Treatment duration
CONTROLLED TRIALS FOR HYPERTENSION INDICATION								
Essential Hypertension								
Placebo-controlled, fixed-dose, monotherapy	010 (c)	50, 100, 400 mg QD 25, 50, 200 mg BID	DBP (ABPM) DBP (cuff)	X	Spironolactone (50 mg BID)		Fixed dose (dose ranging)	8 weeks
	049	25, 50, 100, 200 mg	DBP (ABPM) DBP (cuff)	X			Fixed dose (dose ranging)	12 weeks
Active-controlled	020 (c)	50, 100, 200 mg	DBP (cuff) DBP (cuff)	X	Losartan (50, 100 mg)		Titration-to-effect	16 weeks
	019 (d)	100, 200 mg	DBP (cuff) DBP (cuff)		Losartan (50, 100 mg)		Titration-to-effect	16 weeks
	022	50, 100, 200 mg	SBP (cuff) SBP (cuff)		Amlodipine (2.5, 5, 10 mg)		Titration-to-effect	24 weeks
	026	50, 100, 200 mg	DBP (ABPM) DBP (ABPM)		Amlodipine (2.5, 5, 10 mg)		Titration-to-effect	16 weeks
	016	25, 50, 100, 200 mg	DBP (cuff) DBP (cuff)		Enalapril (5, 10, 20, 40 mg)		Titration-to-effect	12 months (e)
	015 (c)	25, 50, 200 mg	DBP (cuff) DBP (cuff)	X	HCTZ (12.5, 25 mg)	HCTZ	Fixed dose (factorial design)	8 weeks
	010 (c)	50, 100, 400 mg QD 25, 50, 200 mg BID	DBP (ABPM) DBP (cuff)	X	Spironolactone (50 mg BID)		Fixed dose (dose ranging)	8 weeks
Placebo-controlled coadministration with other anti-hypertensives	023	50, 100 mg	DBP (cuff) DBP (cuff)	X (f)		ACE-I or A-II antagonist	Titration-to-effect	8 weeks
	024	50, 100 mg	DBP (cuff) DBP (cuff)	X (f)		BB or CCB	Titration-to-effect	8 weeks
Secondary hypertension due to Primary Hyperaldosteronism								
Active-controlled	018	100, 200, 300 mg	DBP (cuff) DBP (cuff)		Spironolactone (75, 150, 225 mg)		Titration-to-effect	16 weeks

Pbo = Placebo; ABPM = ambulatory blood pressure monitoring; DBP = diastolic blood pressure; SBP = systolic blood pressure; HCTZ = hydrochlorothiazide; ACE-I = angiotensin-converting enzyme inhibitor; A-II antagonist = angiotensin II antagonist; BB = beta blocker; CCB = calcium-channel blocker

† All cuff measurements were seated.

(a) All regimens were QD unless otherwise noted.

(b) Criterion for up-titration was: DBP ≥ 90 mmHg in Studies 016, 018, 019, 023, 024, and 026; SBP ≥ 140 mmHg in Study 022, and DBP ≥ 90 mmHg or SBP ≥ 140 mmHg in Study 020.

(c) Studies 010, 015, and 020 had both placebo and active control arms. Study 010 is the only study presented twice in this table

(d) Patients in Study 019 were allowed open-label HCTZ (12.5 or 25 mg) at Weeks 8 and 12.

(e) In Study 016 the primary efficacy endpoint was assessed at Week 24; secondary efficacy endpoint was assessed at Month 12 after forced down titration at Week 24 in patients responding to therapy at Week 24.

(f) Either placebo or eplerenone was added to background antihypertensive therapy.

Figure 9: Sponsor's Table of the Adequate and Well-Controlled Studies

Study grouping	Study	Eplerenone Doses	Main entry criteria/ Primary endpoint	Active control Doses	Open-label additional antihypertensives	Dosing protocol (a)	Treatment duration
Hypertension with complication	017	50, 100, 200 mg QD	DBP (cuff) and LVH (ECG or echocardiogram)/ LVM (MRI)	Enalapril (10, 20, 40 mg QD) OR enalapril 10 mg QD with either eplerenone 50 mg QD, 100 mg QD, or 200 mg QD	HCTZ, amlodipine (b)	Forced Up-titration	9 months
	021	50, 100, 200 mg QD	DBP (cuff) and UACR/ UACR	Enalapril (10, 20, 40 mg QD) OR enalapril 10 mg QD with either eplerenone 50 mg QD, 100 mg QD, or 200 mg QD	HCTZ, amlodipine (b)	Forced Up-titration	24 weeks

Pbo = Placebo; LVH = left ventricular hypertrophy; ECG = electrocardiogram; DBP = diastolic blood pressure; LVM = left ventricular mass; MRI = magnetic resonance imaging; HCTZ = hydrochlorothiazide; UACR = urinary albumin:creatinine ratio

(a) At times designated by each protocol, study drug was increased to the next higher level even if seDBP < 90 mmHg, unless hyperkalemia or symptomatic hypertension was present.

(b) HCTZ and amlodipine were optional additional medications for all treatment arms after Week 8 as needed, to achieve seDBP < 90 mmHg.

Criterion for use of additional antihypertensive medication was DBP ≥ 90 mmHg (or SBP > 180mmHg in Study 017).

If BP was uncontrolled at Week 8, HCTZ 12.5 mg could have been added, if needed.

If BP was uncontrolled at Week 10, HCTZ could have been increased to 25 mg if HCTZ was started at Week 8 or HCTZ 12.5 mg could have been added if HCTZ was not started at Week 8, if needed.

At Week 12 or thereafter, HCTZ 12.5 mg could have been added if not started previously or the dose of HCTZ was increased to 25 mg if started previously, or amlodipine 10 mg was added if patient was receiving HCTZ 25 mg.

Figure 10: Sponsor's Table of the Other Controlled Studies (Non-BP Endpoints)

Study grouping	Study	Dose (a)	Main entry criteria/ Primary Endpoint	Pbo control	Active control (doses)	Co-administration	Dosing protocol (b)	Treatment duration
Open-label long-term safety	025	50, 100, 200 mg	DBP and SBP (cuff)/ % withdrawn due to treatment failure	None	None	Various antihypertensives (if BP uncontrolled with 200 mg dose)	Titration-to-effect	14 months

(a) All regimens were QD.

(b) Criterion for up-titration was DBP ≥ 90 mmHg or SBP ≥ 140 mmHg.

Figure 11: Sponsor's Table of the Uncontrolled Study

As a one-page guide to the trials, the reviewer prepared the following table:

Table 2: Reviewer's Table of the Fourteen Clinical Studies in Hypertension

#	Contrast	N	Arms	Dose	Control	Co-drugs	Dosing	Weeks
Placebo Control								
049	Dose ranging	390	5	25, 50, 100, 200	Placebo		Fixed	12
Placebo & Active Control								
010	Dose ranging QD vs BID	389 *	8	50, 100, 400 QD/BID	Placebo Spironolactone 50 BID		Fixed	8
015	Dose ranging With/vs HCTZ	612	12	25, 50, 200	Placebo HCTZ 12.5, 25	HCTZ 12.5, 25	Factorial	8
020	Vs losartan Black/white 2:1	535	3	50-200	Placebo Losartan 50-100		Titrate	16
Active Control								
022	SBP Vs amlodipine	260	2	50-200	Amlodipine 2.5-10		Titrate	24
026	Vs amlodipine	143	2	50-200	Amlodipine 2.5-10		Titrate	16
016	Vs enalapril	494	2	25-200	Enalapril 5-40		Titrate	52
018	1^0 aldosteronism Vs SL	137	2	100-300	Spironolactone 75-225		Titrate	16
019	Low renin Vs losartan	161	2	100-200	Losartan 50-100	HCTZ As needed	Titrate	16
Other Antihypertensive Background								
023	With ACEI/ARB	336	4	50-100	ACEI, ARB	ACEI ARB	Titrate	8
024	With BB/CCB	268	4	50-100	BB, CCB	BB CCB	Titrate	8
Non-BP Primary Endpoint								
017	LVH With/vs enalapril	197	3	50-200	Enalapril 10-40	HCTZ amlodipine	Forced	36
021	Albuminuria In diabetics With/vs enalapril	265	3	50-200	Enalapril 10-40	HCTZ amlodipine	Forced	24
Open Label Long Term								
025	Open label Long term	586	1	50-200		Various	Titrate	60

HCTZ = hydrochlorthiazide; SL = spironolactone; BB = beta blocker; ACEI = ACE inhibitor;
ARB = angiotensin receptor blocker; CCB = calcium channel blocker; LVH = left ventricular hypertrophy
Dosages are in mg and all dosing was QD except where specified as BID
* excluding 20 patients from center US0003 that failed DSI inspection

C. Postmarketing Experience

Eplerenone has never been marketed.

D. Literature Review

The NDA includes a general bibliography of 161 publications. These publications cover a wide range of topics from specific articles on eplerenone to classic articles regarding general topics such as aldosterone effects on the cardiovascular system, QT interval prolongation, and the effects of grapefruit juice on CYP3A4. These publications are useful for understanding the potential effects and benefits of eplerenone. They do not provide any additional data relevant to the documentation of the safety and efficacy of the drug.

A Medline search performed on February 7, 2002, for "eplerenone OR SC-66110" yielded 18 references. The majority were commentaries on the potential usefulness of eplerenone or simple summaries of the sponsor's preliminary findings and plans for the drug. No data or findings beyond those included in the application were found in these 18 references.

An Embase search performed on February 7, 2002, for "eplerenone" citations from 1966 through 2002 yielded 41 references. In addition to the commentaries and summaries identified by the Medline search, Embase also returned general articles on aldosteronism. As for the Medline search, no data or findings beyond those included in the application were found in the 41 references reported by Embase.

To define better the potential toxicities of gynecomastia, hyperkalemia, and carcinogenesis for eplerenone and the related drug spironolactone, additional Medline searches were performed on February 7, 2002, for "spironolactone AND gynecomastia" (56 references), "spironolactone AND hyperkalemia" (127 references), "spironolactone AND carcinogen*" (7 references), and "spironolactone AND cancer" (302 references). The vast majority of the references for "spironolactone AND cancer" related to the potential for treating hyperaldosteronism or hormonally-related cancers with spironolactone. A few references addressed associations between cancers and drug use from epidemiological studies, and an IARC monograph on spironolactone carcinogenicity was identified. All of the relevant references from these four searches are summarized above in Section I.E.

V. Clinical Review Methods

A. How the Review was Conducted

The NDA includes fourteen clinical studies for the hypertension indication. Two of the studies, 010 and 049, were randomized, fixed dose, double blind, placebo-controlled trials having a primary efficacy endpoint of changes in seated DBP from baseline. These trials are considered to be the pivotal studies for this NDA. The reviewer analyzed the raw data for these trials provided in the NDA's electronic case tabulations. These two trials are also the focus of the FDA's statistical review. The reviewer duplicated the sponsor's primary analyses from the raw data as well as performing other pertinent analyses not presented by the sponsor. The reviewer confirmed that the sponsor's analyses corresponded to the data in the electronic case tabulations.

A third trial, 015, also was fixed dosing and included a placebo control. It was a factorial design of eplerenone and hydrochlorothiazide alone and coadministered. Because this trial should provide additional confirmation of efficacy vs. placebo and because it addresses the important issue of combination therapy [redacted] the reviewer also reviewed this trial in detail.

The other studies targeted special populations or secondary endpoints. For these studies the reviewer confirmed that the sponsor's primary endpoint results were consistent with the electronic case tabulations. The reviewer also performed some special analyses not generated by the sponsor and checked some of the interesting secondary analyses but otherwise worked from the sponsor's analyses for these studies. The reviewer also examined the sponsor's discussions and interpretations in the study reports and in the sponsor's Integrated Summary of Efficacy.

For safety evaluations the reviewer relied primarily upon the adverse event tabulations (SYM files) and the laboratory test results (LAB and other specialized lab files) in the electronic case tabulations. AEs were coded by the sponsor using the WHO system. The reviewer examined the texts for AEs as reported by the investigator and recategorized the AEs in some cases to represent better the pattern of toxicities. The reviewer referred to the sponsor's tabulations of AEs to contrast with the reviewer's findings regarding serious events and to characterized minor AEs. The reviewer examined the AEs by trial particularly for AEs resulting from drug combinations and for special populations. The reviewer also analyzed patterns of AEs across all of the studies.

B. Overview of Materials Consulted in Review

The reviewer relied upon the materials submitted for this NDA. The IND was not consulted. As noted above, the reviewer used the electronic submissions extensively.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The reviewer checked the internal consistency of the NDA by frequently comparing the text of the NDA and the electronic case report tabulations to the case report forms (provided as electronic copies of the hand-written forms), by reproducing the sponsor's analyses from the electronic case report tabulations, and by comparing the coding of AEs to the investigator's text. The reviewer always could reproduce the sponsor's analyses from the electronic case report tabulations. The coding of AEs also appeared to be extremely accurate, with only one error noted: a handwritten "asthenia" (reviewer's reading) was coded as "asthma".

The only bothersome inconsistency that the reviewer found was that the narratives for SAEs in at least three cases (015-39850795, 021-04622438, and 025-50010001) described the drug as being stopped at the last visit 1-5 weeks prior to the SAE while the case report forms do not document that the drug was stopped nor do they describe any reasons that the drug should have been stopped. In one case the SAE was not included in the sponsor's tabulations but was mentioned in the text. All AEs, before, during, and after treatment and including these three, were recorded in the electronic case report tabulations, so the reviewer relied upon the electronic files rather than the sponsor's tables.

The Division of Scientific Investigations (DSI) attempted to audit four sites picked as higher volume sites in the U.S. for the two pivotal studies. DSI could not audit one site because the records were allegedly lost due to water damage and mold during storage. That site, US0003, contributed 20 patients (4.8 percent) to the pivotal Study 010. The data from site US0003 appeared to be fairly typical of the overall study data for both efficacy and safety. Excluding this site does not affect any results significantly. The other three audited sites had acceptable audit results.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials appear to have been conducted in accordance with accepted ethical standards. Protocols and informed consent forms were approved by institutional review boards (IRB). The protocols include a Regulatory Requirements Appendix that specifies requirements for IRB approval and references FDA regulations and the Declaration of Helsinki. The risks to the patient in the trials appear to have been minimal and explained adequately in the informed consent documents. Monitoring for patient safety appears to have been adequate.

E. Evaluation of Financial Disclosure

One subinvestigator on Study 049 filed a Form FDA 3455 and disclosed [redacted] Two other investigators of 53 on Study 049 failed to submit financial information to the sponsor. No reportable financial disclosures were recorded for the other pivotal study, 010. 44 investigators on other studies failed to submit financial information to the sponsor, including 27 investigators on Study 015, a study that showed a large placebo effect and did not support the efficacy of eplerenone. The virtually complete disclosures for the pivotal studies without significant financial conflicts suggest that financial interests did not influence the primary efficacy results.

APPEARS THIS WAY
ON ORIGINAL

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Two adequate and well controlled studies demonstrated that eplerenone in dosages ranging from 50 to 400 mg daily significantly reduces diastolic and systolic blood pressure in patients with essential hypertension. Eplerenone shows a dose-response relationship from 25 through 400 mg, but excessive hyperkalemia at the 400 mg daily dosage led to the sponsor recommending the dosage range of 50 to 200 mg daily. ABPM data show that once daily eplerenone controls BP throughout the day. The sponsor has proposed the labeling claim that eplerenone "is an effective antihypertensive agent [redacted]" The data do not support the conclusion that eplerenone is equally effective in blacks and whites.

B. General Approach to Review of the Efficacy of the Drug

The general approach to the review of both efficacy and safety is described above in Section V.A. The reviewer analyzed the pivotal Studies 010 and 049 in detail as well as the potentially supportive Study 015. For the critical primary endpoints the reviewer generated independent analyses of the data in the electronic Case Report Tabulations. The reviewer analyzed the other studies in less detail but still confirmed the primary endpoints and other analyses of special interest.

The reviews for all studies are provided in Appendix B. The general issues that were addressed in more than one study are addressed with additional combined analyses in Sections VI.D, XIII, and IX below. Special issues targeted by only one study are also summarized in the appropriate one of those sections.

C. Detailed Review of Trials by Indication

The detailed reviews of the fourteen clinical trials for the hypertension indication are provided in Appendix B. The reviewer did not review in detail other clinical studies for pharmacokinetic purposes but relied upon the FDA biopharmaceutist's review. No information on the PK studies is provided in Appendix B. Each of the trials has a focus that differs from all other studies. The trial focuses are discussed individually in Appendix B and the results are integrated by efficacy topic immediately below.

1. Blood Pressure Reduction

The primary endpoint in both pivotal trials was change from baseline in trough seated cuff DBP. Study 010 was a dose ranging trial in 409 (389 after center US0003 is

excluded) 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 dose ranging in 390 adults with essential hypertension. It tested fixed first morning QD dosages 25, 50, 100, and 200 mg against placebo.

Both studies demonstrated that eplerenone produces statistically significant reductions in DBP. The FDA statistical reviewer's tables are an excellent summary of the primary efficacy results of these trials and they are included below.

Table 3: Statistical Reviewer's Mean Changes in BP for Study 010

Variable	Treatment group							
	Placebo	EP QD (mg)			EP BID (mg)			Spirono-lactone 50 mg BID
		50	100	400	25	50	200	
N	52	54	48	54	53	53	48	47
SeDBP								
Baseline	101	101	101	102	101	101	102	101
Final	100	96	96	93	97	94	93	91
Obs. Mean Change		-4.4	-4.5	-8.9	-4.5	-7.8	-9.4	-9.5
SE	1.0	1.0	1.2	1.1	1.2	1.2	1.1	1.5
Adj. Mean Change	-1.1	-4.5	-4.4	-8.7	-4.4	-7.8	-8.9	-9.5
SE	1.1	1.1	1.2	1.1	1.1	1.1	1.2	1.2
P-value		0.027	0.036	<0.001	0.031	<0.001	<0.001	
SeSBP								
Baseline	153.6	155.6	153.5	151.8	155.8	153.8	155.4	155.1
Final	155.6	150.9	145.5	137.7	146.9	142.0	139.6	137.5
Obs. Mean Change	2.0	-4.6	-8.0	-14.1	-8.9	-11.8	-15.8	-17.6
SE	1.8	2.0	2.1	2.0	1.9	2.3	2.2	2.1
Adj. Mean Change	1.6	-4.4	-7.9	-15.0	-8.0	-11.7	-14.8	-16.7
SE	1.8	1.8	1.9	1.8	1.8	1.8	1.9	1.9
P-value		0.022	<0.001	<0.001	<0.001	<0.001	<0.001	

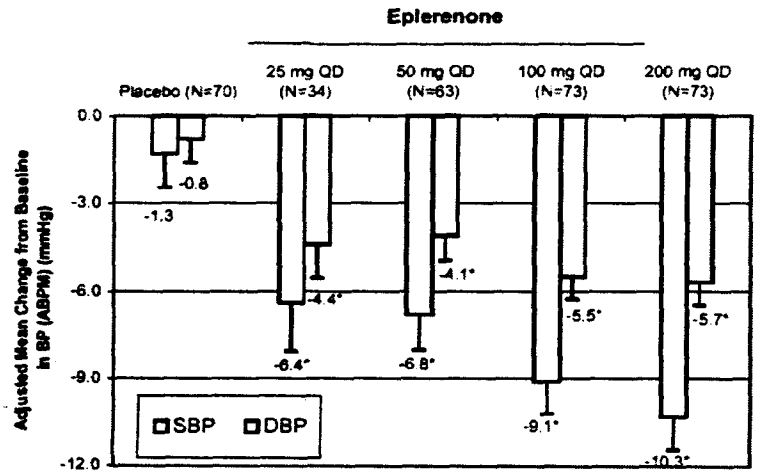
Table 4: Statistical Reviewer's Mean Changes in BP for Study 049

Variable	Treatment group (placebo or daily eplerenone dose)				
	Placebo	25 mg	50 mg	100 mg	200 mg
N	87	45	83	88	87
SeDBP					
Change	-1.7	-3.7	-4.6	-6.3	-5.4
SE	0.9	1.2	0.9	0.9	0.9
1-sided P-value		0.098	0.011	<0.0005	<0.0005

Variable	Treatment group (placebo or daily eplerenone dose)				
	Placebo	25 mg	50 mg	100 mg	200 mg
2-sided P-value		0.198	0.022	0.0002	0.0006
SeSBP					
Change	0.0	-5.7	-6.7	-10.4	-8.8
SE	1.4	2.0	1.5	1.4	1.4
1-sided P-value		0.011	0.0007	<0.0005	<0.0005

All reductions in trough seated cuff BP were statistically significant except for DBP with the 25 mg QD dosage. The treatment effects were reasonable, with placebo-subtracted reductions ranging from –3.4 to –7.8 mm Hg DBP and –5.0 to –16.6 mm Hg SBP for the dose range 50 to 400 mg daily. Note that the reductions with spironolactone 50 mg BID were comparable to those with eplerenone 400 mg daily. One possible inconsistency is that the 400 mg dosage showed greater response in Study 010 while the 100 and 200 mg dosages produced similar reductions in Study 049. Dose-response relationships are explored further in the next section.

Both Study 010 and 049 also employed ambulatory blood pressure monitoring (ABPM) for 24 hours at baseline and at final visit. The ABPM results are very similar to those obtained with cuff measurements, showing slightly greater consistency and differentiation of the values, e.g., the reduction in mean 24-hour DBP for the 25 mg dosage is significantly different from placebo. A summary of mean 24-hour BP changes for Study 049 is shown in the figure below and the ABPM results from Study 010 are discussed in the Dosing Interval section.



*Statistically significantly different from placebo ($p \leq 0.006$).

Figure 12: Sponsor's Change in Mean 24-hour BP by ABPM at Week 12 for Study 049

Study 015 was the other placebo-controlled, fixed dose study. It was an 12-armed factorial study of eplerenone 25, 50, and 200 mg QD, hydrochlorothiazide (HCTZ) 12.5 and 25 mg QD, and placebo in adult patients with mild to moderate essential hypertension. Only the eplerenone/HCTZ 25 and the eplerenone 200/HCTZ 12.5 combinations reduced DBP more than placebo. Only the eplerenone 200/HCTZ 25 combination reduced DBP more than the corresponding monotherapies. The SBP results were a slight variation, with the eplerenone 200 and HCTZ 25 monotherapies and all combinations except the lowest eplerenone 25/HCTZ 12.5 beating placebo and only the eplerenone 50/HCTZ 12.5 beating the corresponding monotherapies.

The explanation of these relatively negative results is that this study showed an unusually large placebo effect, an unadjusted mean change of –7.2 in DBP and –5.2 in SBP. The treatment arms had reasonable mean unadjusted reductions as shown in the table below.

Table 5: Sponsor's Mean Changes in Seated Cuff SBP/DBP for Study 015

	Placebo	E 25	E 50	E 200
Placebo	-5.2/-7.2	-6.6/-7.3	-7.0/-8.0	-12.6/-8.7
HCTZ 12.5	-7.0/-7.7	-10.2/-8.3	-14.6/-8.8	-16.6/-10.9
HCTZ 25	-14.5/-8.9	-17.0/-11.2	-18.2/11.0	-16.6/-12.1

E = Eplerenone; HCTZ = hydrochlorothiazide (From Table T5.1)

While the unusually large placebo effect may explain the negative results, there is no obvious explanation for it. This was a multi-country trial, so the reviewer examined treatment effects by country and did not find any clear patterns—the reviewer's results are given in Appendix B.3. One difference in trial conduct between this trial and Studies 010 and 049 is that the latter two studies included ABPM and an inclusion criterion that the baseline mean 24-hour DBP by ABPM exceed 85 mm Hg. This inclusion criterion may have helped to exclude patients with mildly elevated cuff readings that regressed to the mean during the treatment period.

All other trials showed significant reductions in BP from baseline to final visit with eplerenone. However, because the other trials lacked pure placebo groups, the relevance of the reductions to simple efficacy is impossible to assess. All of the other trials had other contrasts than simple efficacy to placebo, such as comparisons to other drugs or in patient or disease subgroups. The other trial results are summarized in the Interactions with Other Drugs and Special Populations sections below.

2. Dose-Response

Both Studies 010 and 049 show dose-response relationships between eplerenone and BP reduction in the dose ranges studied. The sponsor provided good analyses of the dose-response relationships in the NDA. The sponsor's graphs of the relationships from these two studies are shown below.

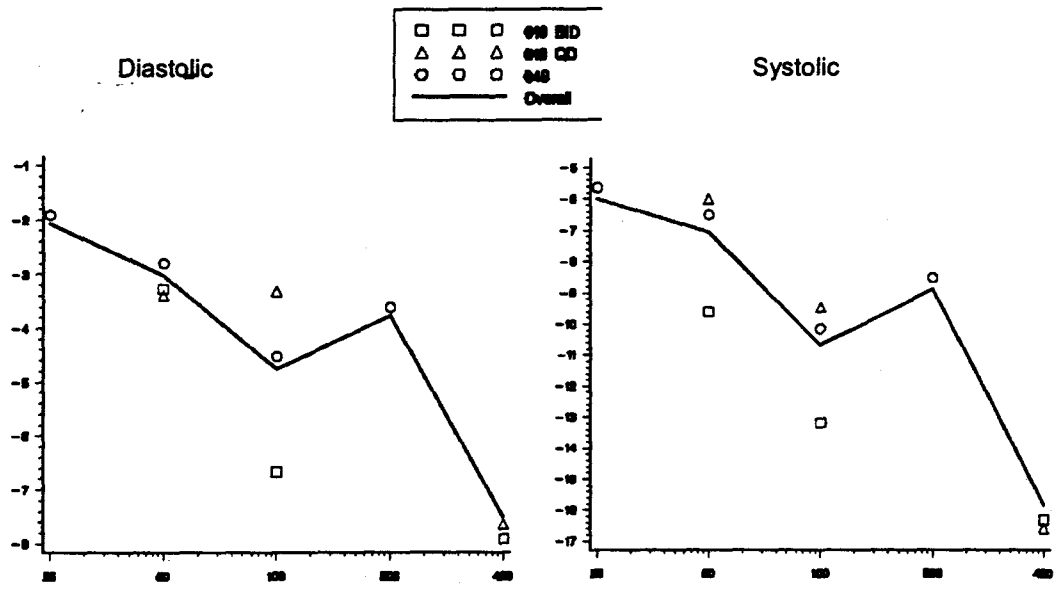


Figure 13: Sponsor's Placebo-Adjusted Trough Cuff BP Response in Studies 010 and 049 (Figures 7.c and 7.d)

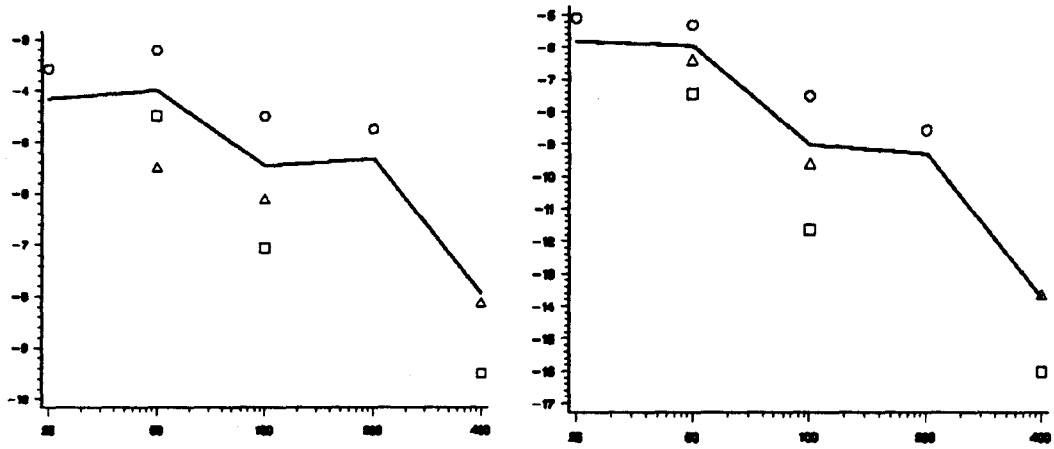


Figure 14: Sponsor's Placebo-Adjusted Mean 24-hour BP Response in Studies 010 and 049 (Figures 7.g and 7.h)

Ignore the lines on the graphs above and compare the series of points. (How the lines were generated is unclear: It would seem logical to have the lines pass through the mean BP for each dosage. This clearly was not done because the lines do not pass through the points for dosages with a single point, e.g., 25 mg or 200 mg.) There is a suggestion of

log-linear dose responses for the 010 QD (triangles) and 049 QD (circles) series, although the 200 mg dosage for 049 appears to be an outlier or suggestive of a lesser slope for 049. The series for 010 BID (squares) suggest a more curvilinear dose-response relationship with flattening of the response at higher dosages. The BP reductions are slightly greater for the BID dosing than for the QD dosing at the same total dosages per day.

The sponsor excluded Trial 015 from the dose-response analyses because of the large placebo effect. The BP reductions in Trial 015 for the eplerenone monotherapy and placebo arms show a dose-response relationship for SBP but not for DBP. The reviewer agrees that it is reasonable to exclude this trial from dose-response analyses because of the unusual placebo effect.

All trends in BP are statistically significant by ANCOVA. The FDA statistical reviewer noted the following about the dose-response relationships:

For Study 010: "There is a suggestion of an increasing effect with increasing dose and to further quantify this relationship, a model was fit using the same model as in the primary analysis, but with a quadratic term for dose. Separate models were fit for the QD regimens and the BID regimens. The coefficient of the quadratic term in the regression model for the QD regimens was not significant ($p = 0.21$). This suggests that the doses for the QD regimens are in the part of the dose response curve where increasing the dose can still gain a proportional increase in response. However, when the model was fit to the BID regimens, a significant quadratic term was found ($p=0.0008$). Since the estimate of this coefficient is positive, this suggests that there may be less additional effect on the response with incremental changes in the dose in the dose range studied."

For Study 049: "There is a suggestion of an increasing effect with increasing dose and to further quantify this relationship, a model was fit using the same model as in the primary analysis, but with a quadratic term for dose. A significant quadratic term was found ($p=0.006$). Since the estimate of this coefficient is positive, this suggests that there may be less additional effect on the response with incremental changes in the dose in the dose range studied. This is contrary to what was found in Study 010 for the once daily regimens studied at doses of 50 mg, 100 mg, and 400 mg."

The FDA biopharmaceutist modeled the dose-response relationship for the Study 010 and 049 data extensively. He documented that an Emax model best fits the data. Please see his review for the details.

Both ends of the proposed dosage range are of particular interest. The lowest dosage tested, 25 mg QD, was not statistically significantly different from placebo for trough cuff seated DBP changes from baseline. It was for cuff SBP and for 24-hour mean BP by ABPM. The 25 mg points on the graphs above are consistent with the rest of the points. They suggest a small effect of 25 mg on trough DBP (about –2 mm Hg) with a greater effect upon mean 24-hour DBP (about –3.5 mm Hg). The effects upon SBP are more similar between trough and mean 24-hour, about –5.6 and –5.0 mm Hg. The sponsor is

proposing 50 mg QD as the recommended starting dose. This recommendation appears reasonable.

At the high end of the dosing range, the reductions in BP for the 200 mg dose in Study 049 appear to be anomalously low. The reductions for the low doses (25 and 50 mg) are consistent with the highest dose (400 mg). No other studies included a pure placebo control, but Studies 017 and 021 specified a forced titration from 50 to 100 (at week 2) and to 200 (at week 4) before adding other medications at week 8. The changes in BP during this titration period for eplerenone only patients with BPs for all four visits and titrated to 200 mg are shown in the table below.

Table 6: Reviewer's Changes from Baseline SBP/DBP during Forced Titration in Studies 017 and 021

	Last Dosage	Study 017	Study 021
N		56	75
Week 2	50	-10.4/-5.0	-7.1/-5.9
Week 4	100	-16.4/-7.7	-10.9/-7.7
Week 6	200	-15.7/-7.3	-13.9/-9.9
Week 8	200	-19.4/-10.1	-16.6/-11.6

The two-week periods between the initial dosage changes is probably sufficient to show most, but not all, of the effect of the dosage level as will be discussed in the next section. These studies also show a graded response from 50 to 200 mg. The one possible anomaly is the flat response at week 6 in Study 017, again for 200 mg, although the week 8 reductions for Study 017 are comparable to the Study 021 values. Study 017 was in patients with essential hypertension and left ventricular hypertrophy and study 021 was in hypertensive diabetics with proteinuria, so the study populations are not precisely comparable to the placebo-controlled studies. The raw BP reductions are slightly greater than in the placebo-controlled studies.

The reviewer's conclusion from these data is that there is a dose-response relationship for eplerenone dosages from 25 to 400 mg daily and DBP and SBP reduction. As the FDA statistical reviewer noted, "It is unclear whether a plateau in response is reached in the range of doses studied (up to 400 mg QD)." However, the limitation of dosage on the high end is not related to efficacy but to safety as is discussed in the Integrated Summary of Safety.

3. Dosing Interval

The sponsor compared QD and BID dosing in only one trial, Study 010. The sponsor's approach for justifying the dosing interval was to compare the QD and BID dosing regimens for the seated trough cuff measurements and for the ABPM 24-hour and trough means, with trough for ABPM defined as hours 22 to 25 after the last dose. The sponsor's summary of these comparisons is the following:

"Comparisons of QD dosage to BID dosage at each dose level were made for a total of eight BP endpoints which included systolic and diastolic BP for the sitting, 24-hr ABPM, and trough ABPM measures. Each test was a pairwise comparison of the QD dose group to the BID dose group conducted at the two-sided 0.05 level without adjusting for multiplicity.

"Results of the comparisons of QD to BID dose are included in Tables T4.1.1, T6.1.1.1, T6.1.2.1, T6.1.3.1, T6.1.4.1, and T6.1.5.1. P-values less than 0.05 were obtained when testing for the differences between the 50 mg BID and 100 mg QD doses for sitting diastolic BP (0.036) and for the difference between the 200 mg BID and 400 mg QD dose for the trough diastolic and systolic ABPM (0.033 and 0.014 respectively). The other 33 differences tested between QD and BID dosing were non-significant and do not confirm a difference in antihypertensive response between QD and BID dosing at any dose level."

The comparisons of BID and QD for the seated trough cuff and mean 24-hr BPs are displayed graphically in Figures 13 and 14 above. The values are also listed in the table below. Visually the BID dosage points appear to trend lower than the QD dosage points. The one exception is the greater reduction in mean 24-hour DBP with 50 mg QD vs. 25 mg BID.

MEAN CHANGE IN BLOOD PRESSURE (mm Hg) FROM BASELINE AT FINAL VISIT								
	Placebo	Eplerenone QD			Eplerenone BID			Spironolactone
	BID	50 mg	100 mg	400 mg	25 mg	50 mg	200 mg	50 mg BID
Parameter								
Sitting DBP	-1.0	-4.4	-4.5	-8.9	-4.5	-7.8	-9.4	-9.5
Sitting SBP	2.0	-4.6	-8.0	-14.1	-8.9	-11.8	-15.8	-17.6
Standing DBP	-0.7	-3.6	-4.2	-8.1	-4.0	-8.2	-8.0	-9.3
Standing SBP	2.8	-4.3	-8.2	-13.9	-7.6	-12.1	-13.8	-16.1
24-hour ABPM DBP	0.6	-4.8	-6.1	-7.6	-3.9	-7.2	-9.3	-8.9
24-hour ABPM SBP	0.0	-7.1	-9.7	-13.0	-7.4	-12.6	-15.9	-15.7
Trough 24 Hour ABPM DBP	-0.9	-3.9	-6.4	-8.1	-4.8	-7.3	-12.4	-9.7
Trough 24 Hour ABPM SBP	-1.6	-6.5	-10.2	-13.2	-8.7	-12.0	-20.5	-17.3

Figure 15: Sponsor's Mean BP Changes for Study 010

The sponsor did not provide peak-trough comparisons. To examine the effects of the BID and QD dosing regimens, the reviewer worked with the raw ABPM data and developed 24-hour plots of the BP reductions. The reviewer's approach is described in detail in Appendix B.1. The plots are reproduced below.

Note that the QD and BID curves overlap considerably and that both show wide separations from the placebo curves, with the separations increasing as the dosage increases. While the 100 and 200 mg BID curves average slightly above the corresponding QD dosages, the reviewer's overall interpretation is that the eplerenone QD dosages produce good reductions in BP compared to placebo throughout the 24-hour day that are not significantly different from the BID regimens.

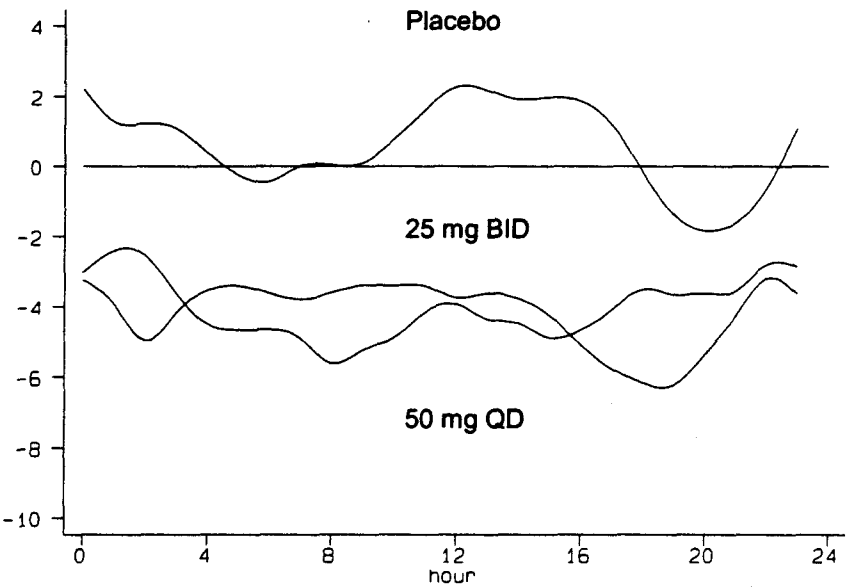


Figure 16: Reviewer's Diurnal Variation in DBP Change from Baseline for Placebo vs. Eplerenone 50 mg Dosages

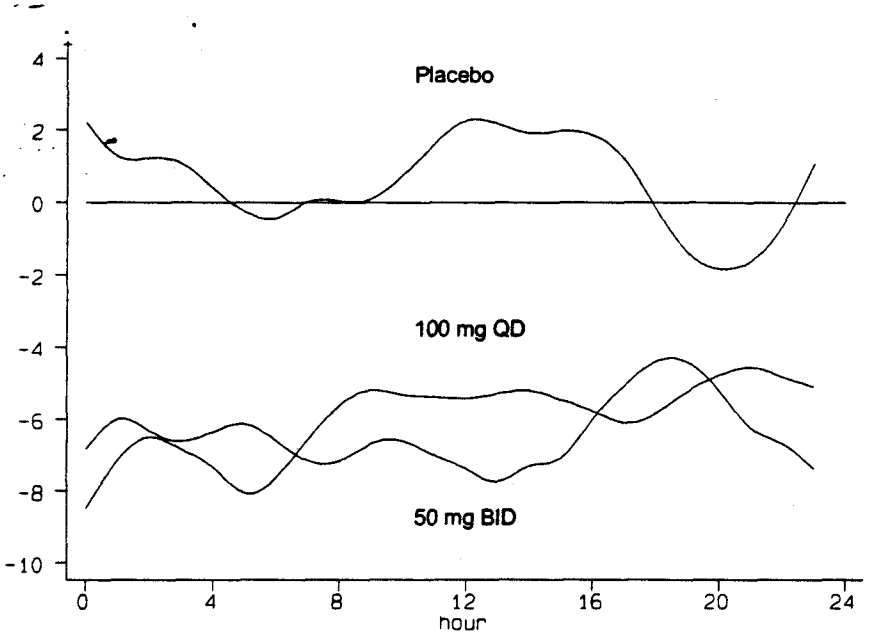


Figure 17: Reviewer's Diurnal Variation in DBP Change from Baseline for Placebo vs. Eplerenone 100 mg Dosages

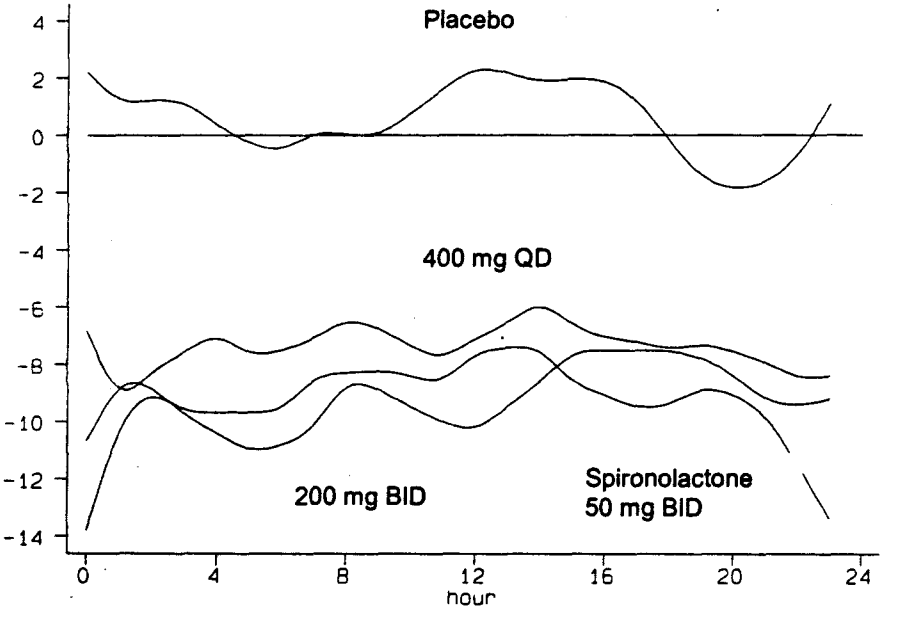


Figure 18: Reviewer's Diurnal Variation in DBP Change from Baseline for Placebo vs. Eplerenone 400 mg Dosages and Spironolactone 50 mg BID

4. Time to Response

Eplerenone's reduction of BP is evident at two weeks and typically fully expressed by four weeks. Plot of the mean BP changes from baseline for the pivotal studies 010 (QD dosages; BID were similar) and 049 are shown in the figures below.

Diastolic

Systolic

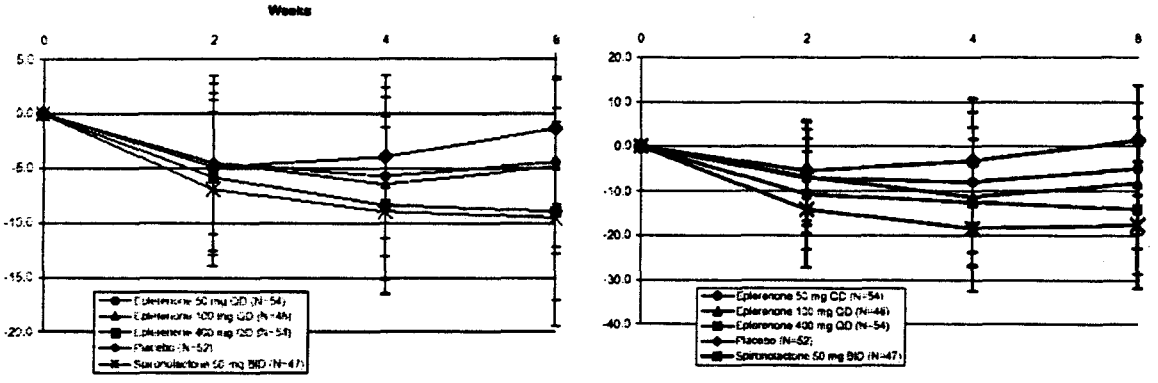


Figure 19: Sponsor's Mean Changes in BP from Baseline by Week for QD Eplerenone Dosing and Spironolactone in Study 010

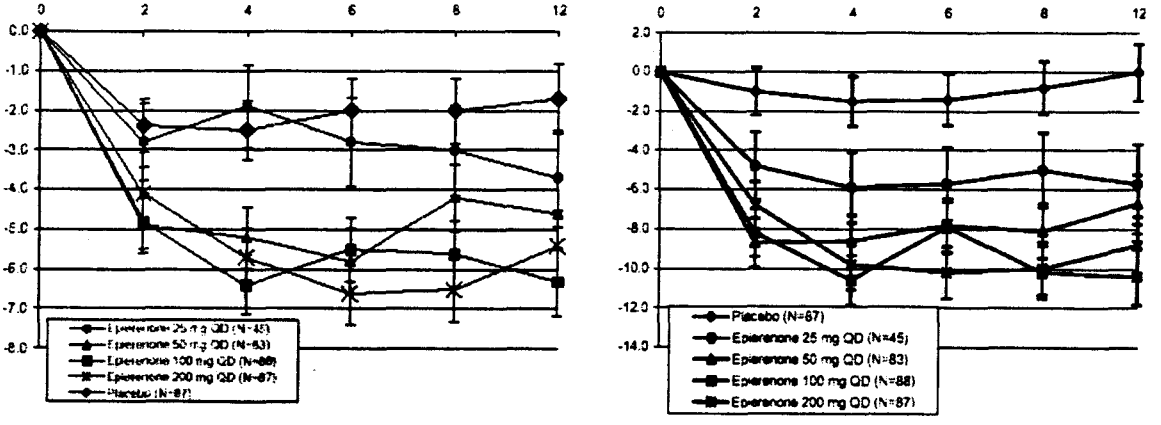


Figure 20: Sponsor's Mean Changes in BP from Baseline by Week for Study 049

5. Maintenance

Five of the studies specified use of eplerenone for at least six months: Studies 016, 017, 021, 022, and 025. In the NDA Integrated Summary of Efficacy the sponsor provides tables of BP changes for these studies to justify the conclusion "The antihypertensive effect of eplerenone was maintained for the duration of these studies, with no evidence of attenuation." In the tables provided the eplerenone BP reduction appears to be maintained well. For example, in Study 016 BP reduction in the eplerenone arm was –15.2/-12.4 at week 12 and –17.4/-15.2 at week 24 (observed values) or -14.6/-11.5 at week 12 and -14.5/-11.7 at week 24 (LOCF). However, the interpretation of the maintenance of BP reduction in these studies is complicated by the following study design limitations: All five studies used titration-to-effect and Studies 017, 021, and 025 also allowed use of other antihypertensives. The sponsor did not provide information on dosages by time.

Study 016, titrated eplerenone vs. enalapril, included a forced down-titration of one level (200 to 100, 100 to 50, and 50 to 25 mg) at six months. In the first month after the forced down-titration, 31.7 percent (51/161) of the eplerenone group and 28.8 percent (44/153) of the enalapril group required re-up-titration. By month 11, 54.0 percent (87/161) of the eplerenone group and 47.7 percent (73/153) of the enalapril group required re-up-titration. The majority of patients taking eplerenone 50 mg at the week 24 primary endpoint did not require re-up-titration after forced down-titration, while the majority of patients taking 100 and 200 mg did.

The longest study was the uncontrolled open-label Study 025. For that study the sponsor summarized the efficacy with withdrawal rates: "Over the course of the study, 98 (16.8%) of the 582 patients in the intent-to-treat population withdrew due to uncontrolled BP. During the first four months, 70 (12.0%) patients withdrew due to treatment failure." Note also that 238 patients (41 percent) required the addition of an additional antihypertensive medication. 219 patients (37 percent) completed the study on eplerenone alone. The time course for BP changes for Study 025 is shown in the following figure.