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APPROVAL PACKAGE FOR:

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Medical Review(s)

**Clinical Review Cover Sheet
Supplemental NDA Submission**

sNDA 21-437
Inspra™ Tablets
Pharmacia Corporation

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

CLINICAL REVIEW

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Clinical Review for sNDA 21-437

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Eplerenone produced a 15% reduction ($p = 0.008$) in mortality in a large trial in patients with congestive heart failure (HF) following acute myocardial infarction (MI). The major potentially serious adverse effect, hyperkalemia, was managed by monitoring potassium levels and adjusting dosage so that rates of serious hyperkalemia were low. From a clinical perspective I recommend approval of eplerenone to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction $\leq 40\%$) and clinical evidence of HF post-MI.

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

I do not recommend any mandatory phase 4 studies. There are unanswered questions regarding eplerenone use that, if elucidated, would help to improve its usability. Some questions are relevant to the HF post-MI indication of this sNDA and others are more relevant to the hypertension indication. Questions relevant to the HF post-MI indication are regarding dosage, dosing interval, duration of treatment, and effectiveness in patients without clinical signs of HF and in the very elderly. Questions relevant to the hypertension indication are whether eplerenone has any effects upon breast cancer incidence, thyroid dysfunction, or adrenal adenoma development. Equally important as these questions is the issue of whether the benefit of eplerenone in HF post-MI extends to other HF populations, i.e., ones not immediately post-MI.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Eplerenone (Inspra™) is an aldosterone receptor competitive antagonist similar to spironolactone. Eplerenone is formulated in tablets for oral administration. It was approved for the treatment of hypertension on September 27, 2002. This sNDA addresses a new indication, the treatment of stable patients with evidence of HF post-MI.

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The clinical program for this new indication included one pivotal study, EPHESUS, a large (6,632 patients), international, randomized, double-blind, placebo-controlled outcomes trial. It also included two small dose-ranging studies in HF and a pharmacokinetics study. The sNDA also includes the data for another large, international study (RALES) of a related drug, spironolactone, for the treatment of class 3 and 4 HF. Data on RALES was included to show supporting evidence that aldosterone blockers improve survival in HF.

The clinical program for the hypertension indication included 13 clinical trials and 1 open label, longer term safety and efficacy study. The hypertension studies included 4,908 patients, both eplerenone treated and controls. Of these 3,106 patients received at least one dose of eplerenone. These studies provide relevant information on eplerenone adverse effects as well as raise some unanswered questions regarding its safety.

B. Efficacy

The efficacy of eplerenone in post-MI HF is demonstrated by the one pivotal study, EPHESUS. EPHESUS was a multinational, multicenter, double-blind, randomized, placebo-controlled study in patients clinically stable 3-14 days after an acute myocardial infarction with left ventricular dysfunction (as measured by ejection fraction $\leq 40\%$) and either diabetes or clinical signs of congestive heart failure (pulmonary congestion by exam or chest x-ray or S₃). Patients with HF of valvular or congenital etiology, patients with unstable post-infarct angina, and patients with serum potassium >5.0 mEq/L or serum creatinine >2.5 mg/dL were excluded. Patients were allowed to receive standard post-MI drug therapy and to undergo revascularization by angioplasty or coronary artery bypass graft surgery.

Patients randomized to eplerenone were given an initial dose of 25 mg once daily and titrated to the target dose of 50 mg once daily after 4 weeks if serum potassium was < 5.0 mEq/L. Dosage was reduced or suspended anytime during the study if serum potassium levels were ≥ 5.5 mEq/L.

EPHESUS randomized 6,632 patients (9.3% U.S.) at 671 centers in 27 countries. The study population was primarily white (90%, with 1% black, 1% Asian, 5% Hispanic, 2% other) and male (71%). The mean age was 64 years (range, 22-94 years). The majority of patients had pulmonary congestion (75%) by exam or x-ray and were Killip Class II (64%). The mean ejection fraction was 33%. The average time to enrollment was seven days post-MI. Medical histories prior to the index MI included hypertension (60%), coronary artery disease (62%), dyslipidemia (48%), angina (41%), type 2 diabetes (30%), acute MI (27%), and HF (15%).

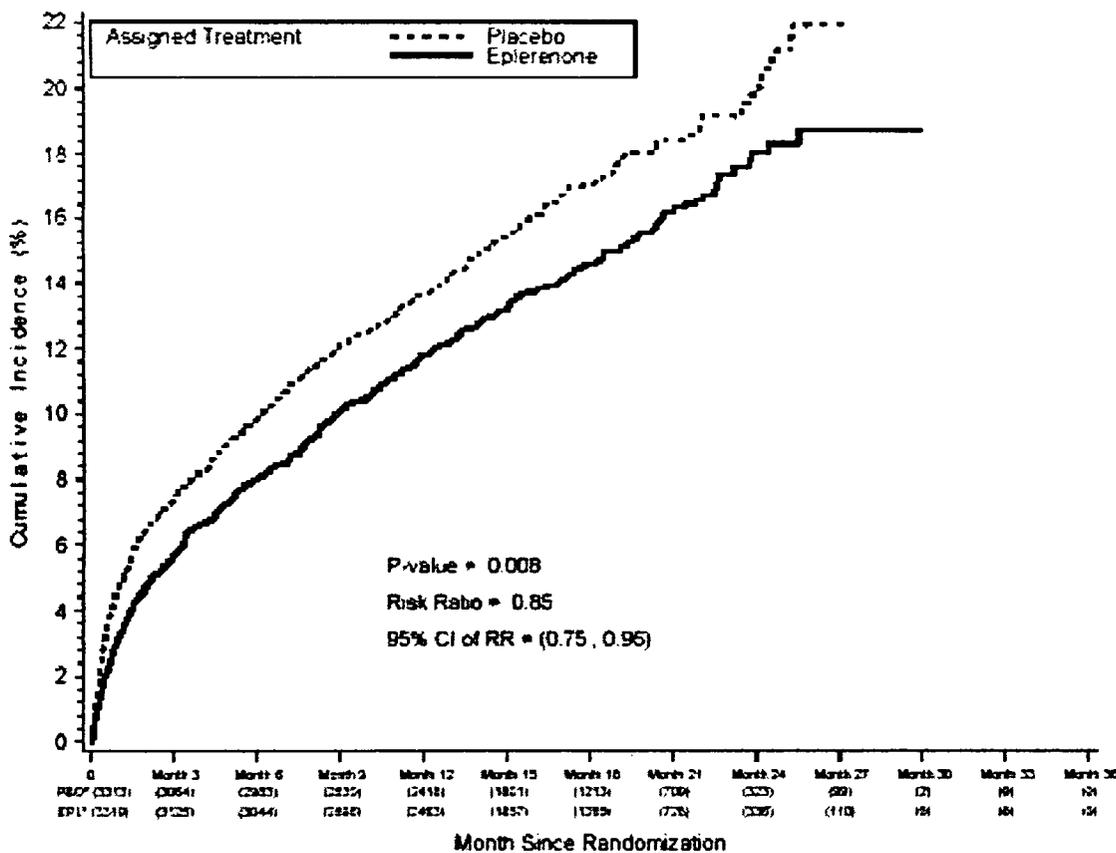
The mean dose of eplerenone was 43 mg/day. Patients also received standard care including aspirin (92%), ACE inhibitors (90%), β -blockers (83%), nitrates (72%), loop diuretics (66%), or HMG-CoA reductase inhibitors (60%).

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Patients were followed for an average of 16 months (range, 0-33 months). The ascertainment rate for survival was 99.7%.

The primary endpoint defined in the original protocol was time to death from any cause. There were 478 deaths in the eplerenone group (14.4%) and 554 deaths in the placebo group (16.7%). The relative risk of death with eplerenone was 0.85 (95% confidence interval 0.75 to 0.96; $p = 0.008$ by logrank test). Kaplan-Meier estimates of all cause mortality are shown in Figure 1. Two-thirds of the difference in deaths occurred within the first 30 days. There was still a mortality benefit of eplerenone beyond 30 days (relative risk 0.92). The major contributor to the difference in deaths was sudden death, although there were also similar relative risk reductions in recurrent MI and HF deaths.



*: Number of Patients at risk

Figure 1: Cumulative Mortality in EPHEBUS

A second primary endpoint, combined cardiovascular (CV) mortality and CV hospitalization, was allocated 0.01 of a. CV mortality was defined as sudden cardiac death or death due to progression of heart failure, stroke, or other CV cause and CV

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hospitalization was defined as hospitalization for progression of heart failure, myocardial infarction, stroke, or ventricular arrhythmia (but not atrial arrhythmia, angina, CV procedures, or other CV causes.) By these definitions time to first event was significantly longer in the eplerenone group (risk ratio 0.87, $p = 0.002$). For CV mortality and all CV hospitalizations, time to first event was not significantly longer with eplerenone than placebo ($p = 0.028$, hazard ratio 0.92). All cause hospitalizations and combined all cause hospitalizations and all cause mortality were not significantly different between the two groups. Rates of patients dying or hospitalized in EPHESUS are provided in Table 1.

Table 1: Rates of Patients Dying or Hospitalized in EPHESUS

Event	Eplerenone n (%)	Placebo n (%)
CV death or CV hospitalization*	1516 (45.7)	1610 (48.6)
CV death†	407 (12.3)	483 (14.6)
CV hospitalization†	1281 (38.6)	1307 (39.5)
All cause death or hospitalization*	1734 (52.2)	1833 (55.3)
Death†	478 (14.4)	554 (16.7)
Hospitalization†	1497 (45.1)	1530 (46.2)

*First event; †Any event

The following subgroup differences are of clinical interest:

- Efficacy appears to be lacking in patients aged 75 and over (eplerenone 27% vs. placebo 26%). That this is a real effect is suggested by the continuous reduction in benefit from younger to older ages and the significance of age as a covariate in Cox regressions.
- Eplerenone was not associated with reduced mortality in diabetics without clinical evidence of HF (eplerenone 16% vs placebo 15%). (Diabetics were the one subgroup that could be eligible without clinical evidence of HF.)
- Eplerenone was not associated with reduced mortality for patients with a baseline history of renal insufficiency (eplerenone 31% vs. placebo 30%) or for patients with a baseline estimated creatinine clearance ≤ 30 ml/min (both 42%). Difference in mortality was small for patients with baseline estimated creatinine clearance of 31-50 ml/min (eplerenone 26% vs. placebo 27%).
- Eplerenone was not associated with reduced mortality for patients without a history of hypertension at baseline (both 14%). Eplerenone was also not associated with reduced mortality for patients with baseline SBP <100 .

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The eplerenone group usually showed lower mortality rates than the placebo group regardless of baseline or concurrent CV drug use. Mortality was slightly higher in the eplerenone group in patients not treated at baseline with beta blockers (24% vs. 23%) and CV mortality was identical (20%). This difference is likely related to the fact that the average age of patients not taking beta blockers was higher than those taking them (67 vs. 63). There is an intriguing relationship that eplerenone benefit after 28 days was only seen in patients receiving a digitalis preparation.

An EPHEBUS quality of life (QoL) substudy using the Kansas City Cardiomyopathy Questionnaire did not show significant differences in improvement in QoL between eplerenone and placebo. Changes in NYHA class were better in the eplerenone group, but differences were small (worsened 25% eplerenone vs 29% placebo) and more than half (62%) of the difference in the worsened category is accounted for by deaths.

EPHEBUS included substudies for a wide variety of CV biomarkers. The substudy results did not confirm a mechanism of action by which aldosterone blockade reduces mortality. While eplerenone increased serum aldosterone levels compared to placebo, the substudies did not show significant differential effects of INSPRA upon collagen markers, cytokines, vascular compliance, fibrinolytic balance, cardiac remodeling, or heart rate variability.

RALES, a study in the related aldosterone blocker spironolactone, provides additional evidence that an aldosterone blocker can improve survival in HF patients. RALES was an international, randomized, double-blind, placebo-controlled, parallel-group study of spironolactone in addition to standard treatment in patients with severe heart failure (ejection fraction \leq 35% and NYHA class 3 or 4 with a history of class 4 within the past six months). Patients had to be taking a loop diuretic and, if tolerated, an ACE inhibitor.

RALES enrolled 1,663 patients at 195 sites in 15 countries. Only 3% of the patients were from the US. The patients were predominantly white (87%) and male (73%). The average age was 65 with 21% \geq 75. The mean ejection fraction was 0.26 and 69% were NYHA class 3.

Patients randomized to spironolactone were given 25 mg daily. The dosage could be increased to 50 mg daily at the discretion of the investigator. The average dosage was 26 mg.

The study was terminated on August 28, 1998, by the DSMB based on a stopping rule for mortality differences. Median follow-up in RALES was 103 weeks. The ascertainment rate for vital status was 96%.

In RALES spironolactone reduced the risk of death by 30% compared to placebo ($p < 0.001$). The survival curves do not start to diverge until three months, but the divergence thereafter is impressive. Spironolactone reduced mortality from both sudden death and

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from progression of HF. The major contributor was reduction in deaths from HF rather than sudden death.

Total non-fatal hospitalizations were significantly less frequent in the spironolactone group (51%) than in the placebo group (57%). The difference is largely due to fewer hospitalizations for HF aggravated with spironolactone. NYHA class changes were significantly better in the spironolactone group.

One of the most striking findings in RALES is the relationship of CV mortality to baseline serum potassium levels as shown in Figure 2.

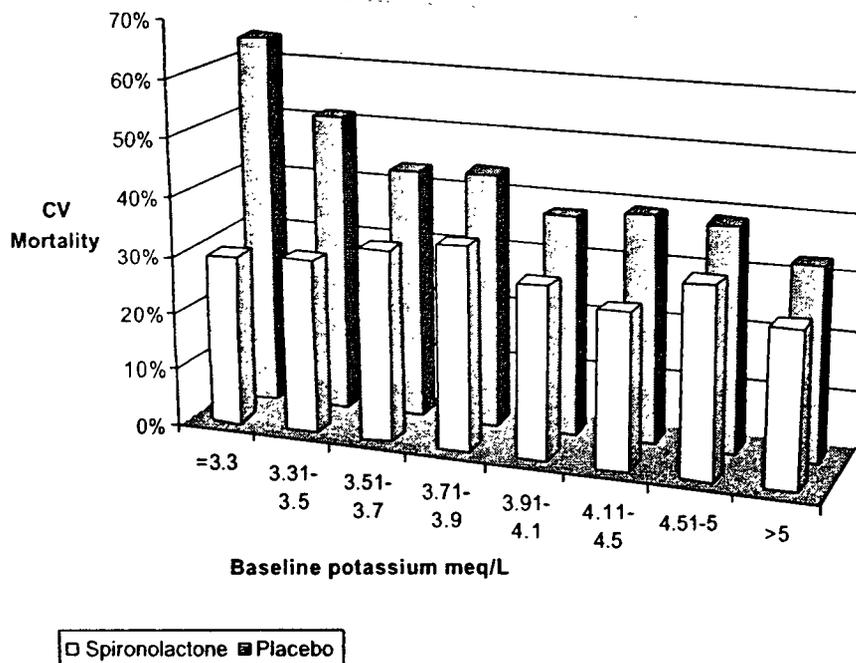


Figure 2: CV Mortality by Baseline Potassium Level in RALES

CV Mortality with placebo increased as baseline potassium level decreased while CV mortality with spironolactone did not vary greatly across the range of baseline potassium levels. Note that in RALES all patients were on a loop diuretic. In EPHEsus CV mortality during the entire study showed a U-shaped relationship to potassium levels in both treatment groups, with eplerenone showing a mortality benefit at all potassium levels except the two extremes. However, 28-day CV mortality shows a similar pattern to that in RALES as shown in Figure 3.

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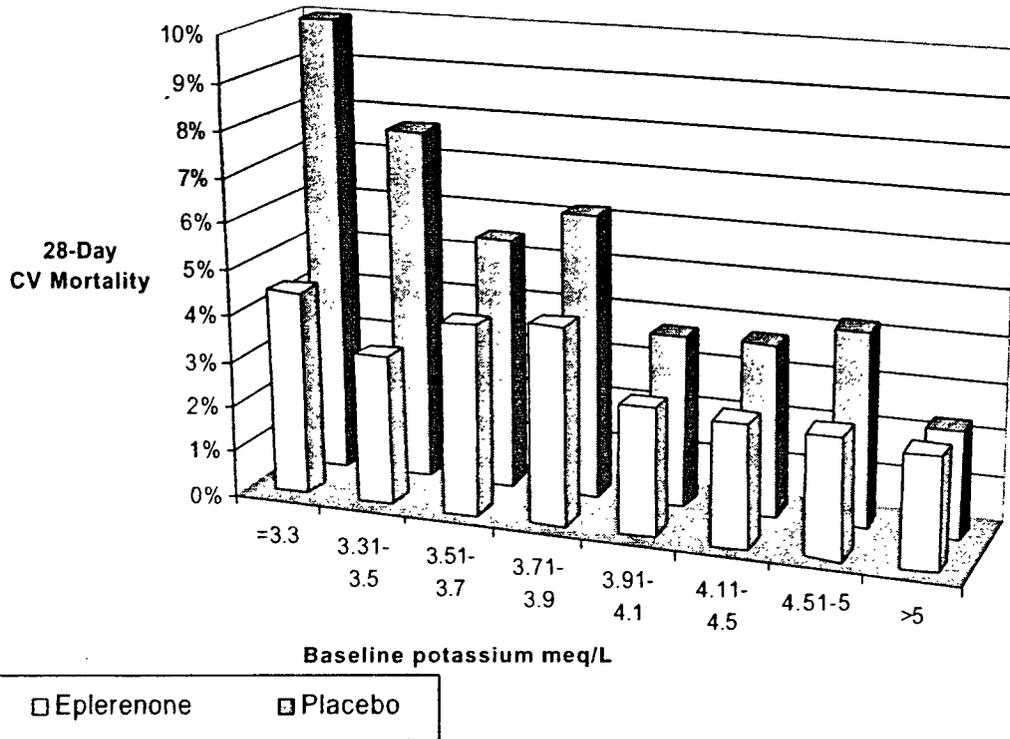


Figure 3: 28-Day CV Mortality by Baseline Potassium Level in EPHESUS

There are few patients (<100 in the eplerenone group) in the two extreme potassium categories. The baseline values in EPHESUS were obtained during the immediate post-MI period, a period of instability, so that they do not reflect basal or usual values for the patients or body stores of potassium. In EPHESUS there were an excess of 38 placebo sudden and MI deaths in the first 28 days compared to 17 during the rest of the study, while placebo HF death excesses were slightly greater post-28 days (13 vs. 10). The 28-day CV mortality benefit was unrelated to measures of HF such as pulmonary congestion.

The relative risks of CV death for eplerenone (28 days) and spironolactone (entire study) compared to placebo by baseline potassium levels are similar as shown in Figure 5. The reduction in risk for both drugs is greatest for lower baseline potassium levels, although there is substantial risk reduction for all baseline potassium levels except perhaps the highest level for eplerenone. This relationship of increased risk reduction with lower baseline potassium levels combined with the reduction in sudden deaths shown in EPHESUS suggests that some of the risk reduction is due to lowered risk of fatal arrhythmias related to reduction of hypokalemia. One would expect that the risk of arrhythmic death in EPHESUS is greatest in the immediate post-MI period. In RALES, with more severe HF and universal treatment with loop diuretics, one would expect that the risk of arrhythmic death extends throughout the trial.

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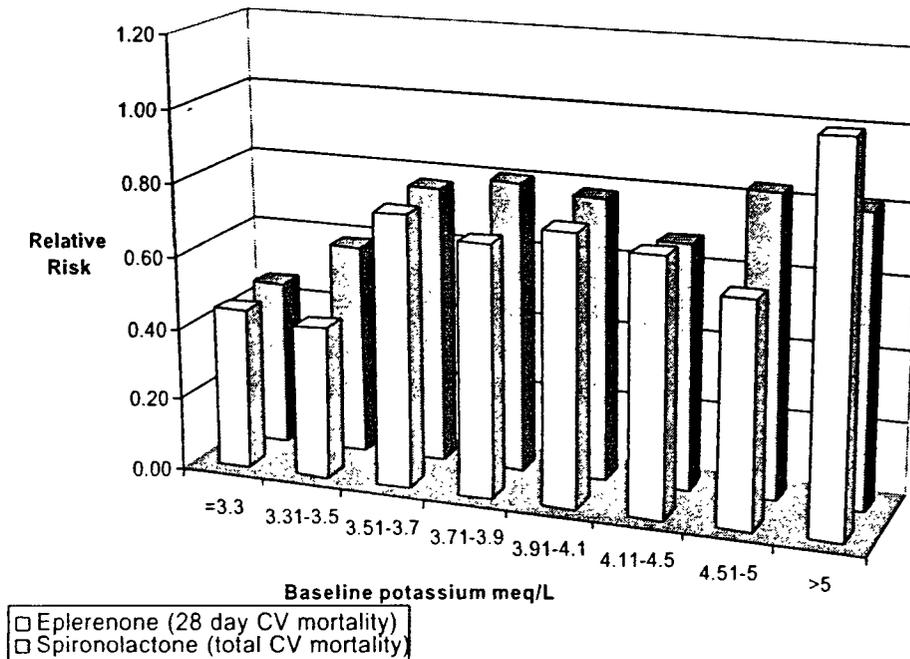


Figure 4: Relative Risk of CV Death Compared to Placebo by Baseline Potassium Level in EPHESUS and RALES

The new indication is supported by only one pivotal trial, EPHESUS. However, the primary indication is vital, improved survival, and the statistical significance of the survival improvement is high ($p = 0.008$) such that EPHESUS alone is adequate for supporting approval of the new indication. RALES provides additional reassurance that aldosterone blockers have efficacy in improving survival in heart failure patients. EPHESUS substudies of a wide variety of CV markers do not provide evidence regarding how aldosterone blockage improves survival, but the relationship of mortality to potassium levels and the improvement in sudden deaths suggest that effects upon potassium levels may be important.

C. Safety

EPHESUS provides about 3,800 patient-exposure years (PEY) to eplerenone with a mean dose of 43.5 mg. Study 011 provides an additional 61 PEYs but in particular it provides data on higher dosages (to 200 mg) in HF patients. The hypertension studies provide 1,081 PEYs at doses ranging from 25 to 400 mg.

In EPHESUS overall adverse event rates for eplerenone were similar to placebo (AEs in 79% of eplerenone patients vs. 80% of placebo patients.) Serious AEs were more frequent in the placebo group (51%) than in the eplerenone group (49%), with most of the

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difference due to a lower rate of HF SAEs in the eplerenone group. The noteworthy AEs related to eplerenone in EPHESUS are the following:

- Hyperkalemia was more frequent with eplerenone. Both lab measures of potassium, e.g., any value >5.5 mmol/L in 16% of eplerenone patients and 11% of placebo patients, and reported AEs, e.g., 3.6% of eplerenone patients and 2.3% of placebo patients, were higher in the eplerenone group. Hyperkalemia was more frequent with reduced renal function, e.g., mean increase in potassium was 0.36 mmol/L in eplerenone patients with baseline creatinine clearance (CrCl) ≤ 30 ml/min vs. 0.22 in placebo patients with CrCl ≤ 30 , 0.22 in eplerenone patients with CrCl >100 , and 0.14 in placebo patients with CrCl >100 . Hyperkalemia was also more frequent in patients with a history of diabetes or proteinuria on the baseline urinalysis and most frequent with both and eplerenone treatment. Hyperkalemia was more frequent with ACE inhibitor or angiotensin II receptor blocker use; hyperkalemia SAEs were reported only in patients who received these drugs.
- Hypokalemia was less frequent with eplerenone. Hypokalemia AEs were reported in 0.6% of eplerenone patients and in 1.6% of placebo patients.
- Sex hormone-related adverse events were uncommon and occurred at similar rates in the two treatment groups, e.g., gynecomastia was reported in 0.5% of eplerenone-treated males and in 0.6% of placebo-treated males. The median time to development of gynecomastia in the eplerenone group was 491 days. The low rate of gynecomastia in EPHESUS is likely related to both the dosage and duration of therapy and the lack of specific sex-hormone related AE questions or exams in EPHESUS. With longer durations of therapy or higher dosages gynecomastia could become a patient problem.
- Both hyperthyroidism (0.4% vs 0.3%) and hypothyroidism (0.5% vs. 0.2% placebo) AEs were slightly more frequent with eplerenone treatment than with placebo. Hyperthyroidism and hypothyroidism were also more frequent with spironolactone in RALES. One thyroid cancer was reported in an eplerenone patient. Even if real these thyroid effects would not be greatly troublesome because symptoms can be monitored and TSH levels obtained if there are any suspicions of problems.
- Two adrenal adenomas were reported in eplerenone patients and none in placebo patients. While one was symptomatic, a real increased rate of adrenal adenomas probably needs only physician awareness of the issue. Adrenal "incidentalomas" are not uncommon. A moderately increased rate will be difficult to detect.
- Prostate cancers were reported significantly less frequently in eplerenone-treated males (0.4%) compared to placebo-treated males (0.04%). Breast cancer was only reported in eplerenone females (0.3%). Both of these differences, as well as gynecomastia, are consistent with an estrogen-like effect. While the prostate cancer

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difference is a possible benefit, the breast cancer difference if real is a possible detriment particularly for chronic use in hypertension.

Eplerenone in HF patients post-MI appears to be reasonably safe. The one potentially dangerous adverse effect (AE), hyperkalemia, was controlled in EPHEUS through monitoring of serum potassium levels and dose reduction or suspension for hyperkalemia. Eplerenone effects upon potassium levels may have contributed to its survival benefit. The other troublesome AEs, the sex-hormone related ones, were not more frequent than the placebo rates within the dosage and duration of exposure in EPHEUS, although they did occur with higher doses of eplerenone in Study 011. The EPHEUS data suggest but do not prove some other possible AEs (thyroid dysfunction, adrenal adenomas, and breast cancer) that may be problematic particularly for the hypertension indication.

D. Dosing

EPHEUS used a single dosing scheme. The dose was based on effects upon rennin-angiotensin-aldosterone system hormones relative to spironolactone and the spironolactone dose used in RALES. While the dose selected was reasonable and the results of EPHEUS are favorable regarding both safety and efficacy, the optimal dosing strategy for eplerenone in HF post-MI is not known. Questions remain regarding the optimal dosage, the dosing interval, whether dosing adjustments are needed for special populations, and the duration of treatment. However, because the regimen used was effective and improved a vital endpoint, these questions do not prohibit approval.

E. Special Populations

Efficacy and safety in EPHEUS did not appear to vary by gender. There are some variations by age. The major finding regarding age effects on efficacy was that eplerenone seemed to show reduced efficacy in the very elderly, i.e., age = 75 (eplerenone mortality 27% vs. placebo 26%). The effects in the elderly appear complex: Mortality through 28 days was lower with eplerenone for the elderly ≥ 75 (6% vs. 7%). Mortality was higher with eplerenone for the rest of the study in survivors to 28 days (22% vs. 21%). In contrast, spironolactone in RALES appeared to show increasing efficacy with age. Whether the eplerenone effects in the elderly are real or spurious is impossible to determine from EPHEUS alone. Additional data are needed to determine whether or how patients age = 75 should be treated.

The major finding regarding age effects on toxicity was that hyperkalemia was more frequent in the elderly. The sponsor attributed this effect to the reduced renal function seen in the elderly.

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The sponsor has proposed pediatric studies for the hypertension indication. Myocardial infarction is extremely rare in children, so pediatric studies are not feasible for this new indication.

Regarding race or ethnicity effects, EPHEBUS and RALES were trials predominantly in white males. They were large trials, so sufficient data are available to address basic issues regarding gender effects. They did not include sufficient numbers of blacks to answer definitively whether there are differences in efficacy or safety in blacks. The hypertension trials had equivocal results regarding whether eplerenone is equally effective for treating hypertension in all blacks. While the number of blacks in EPHEBUS is too small to give accurate estimates of a mortality benefit in blacks, it is reassuring that the point estimates of mortality rates in blacks greatly favor eplerenone (eplerenone 13%, placebo 23%).

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B. State of Armamentarium for Indication(s)

The proposed new indication ☐

ACE inhibitors (ACEI) are generally recognized as effective for this indication. (Ryan, Antman et al. 1999) The ACEI captopril has an approved indication for left ventricular dysfunction after MI based on the results of the SAVE trial. (Pfeffer, Braunwald et al. 1992) In SAVE 2,231 patients 3 to 16 days post-MI were randomized to captopril or placebo and followed for a minimum of 2 years, with an average follow-up of 3.5 years. Captopril reduced the risk of all-cause mortality by 19% relative to placebo.

Other drugs are approved or generally recognized effective for related indications. Beta blockers and aspirin are generally recognized to reduce mortality post-MI, e.g., atenolol is approved to reduce cardiovascular mortality post-MI. Both ACEI and beta blockers are approved to reduce mortality in patients with heart failure and reduced left ventricular systolic function. While the use of these drugs and other interventions have led to improvements in survival both post-MI and in HF, both disorders remain deadly, particularly in the elderly: The case fatality rate for MI has been estimated as about 30%. (Kuch, Bolte et al. 2002) Five year survival in elderly patients hospitalized for HF was recently estimated as 36%. (Feinglass, Martin et al. 2003) There is much room for improvement.

C. Important Milestones in Product Development

The sponsor submitted IND 51,780 for eplerenone for the treatment of hypertension on October 24, 1996. After an end-of-phase 2 meeting on July 17, 1998, and a pre-NDA meeting on July 19, 2001, the sponsor submitted the NDA for the treatment of hypertension on November 28, 2001. Eplerenone was approved for the treatment of hypertension on September 27, 2002.

On January 9, 2003, the Division met with the sponsor to discuss the sNDA for HF. In addition to data on EPHESUS, the primary trial supporting the new indication, the sponsor agreed to submit the manuscript, final study report, blank case report forms annotated with SAS data sets and the RALES data for the Randomized Aldactone Evaluation Study (RALES) to support the concept that aldosterone blockade reduces mortality in patients with heart failure. There was a discussion regarding the number of trials needed for approval. The sponsor asked if the data they presented today (EPHESUS study) held up to review, would this support an approval as a single trial separate from the RALES data. The division director explained that on the surface the data are robust; however, the Division could not comment on the approval prior to reviewing the data.

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D. Other Relevant Information

Eplerenone has not been approved for any indication in any foreign country. Eplerenone has also not been denied approval for any indication in any foreign country.

E. Important Issues with Pharmacologically Related Agents

Eplerenone is chemically and pharmacologically similar to another aldosterone receptor inhibitor, spironolactone (Aldactone[®]). The FDA medical review of the original NDA submission reviewed the literature on spironolactone pharmacokinetics and adverse effects in detail. For the details see the medical review posted on the FDA website at http://www.fda.gov/cder/foi/nda/2002/21-437_Inspra.htm. The following is a summary of the information from that review.

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 (10-35 hours) 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. While this warning is based primarily on pre-clinical carcinogenicity studies in rats done many years ago, the question of carcinogenicity of spironolactone has also been raised in post-marketing reports and, as is discussed later in the review, some questions regarding possible carcinogenicity of eplerenone are raised by the data from the large HF trial. Hence the background on spironolactone carcinogenicity is summarized below in detail.

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

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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."(Pharmacia 2002)

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."(IARC 1980)

The epidemiological evidence regarding the carcinogenicity of spironolactone is relevant. Because spironolactone (and possibly 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.(Loube and Quirk 1975)

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 BCDS 1 of 150 breast cancer patients (0.7%) and 6 of 600

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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.(Jick and Armstrong 1975)

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.(Williams, Feinleib et al. 1978)

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 with spironolactone that was not confirmed in by lag-time analyses.(Friedman and Ury 1980)

While these studies are reassuring regarding the carcinogenic potential of spironolactone both for female breast cancer, a case series raises another issue: 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.(Stierer, Spoula et al. 1990) 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. This concern is reinforced by AE reports to the FDA. From 1975 to 2003 there were 11 cases of male breast cancer recorded in the FDA Adverse Event Reporting System (AERS) associated with Aldactone or Aldactazide use. While the rate of reports is extremely low, male breast cancer is rare.

One other cancer type has been noted to be associated with spironolactone in an epidemiological study. A population-based, case-control study of thyroid cancer (159 cases, 285 controls) was conducted in Connecticut.(Ron, Kleinerman et al. 1987) The odds ratio for use of spironolactone was 4.3.

COMMENT: None of the evidence above is absolute proof that spironolactone is carcinogenic. However, the male breast cancer association is suggestive that spironolactone could contribute to the development of estrogen-related tumors and the

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thyroid cancer association is suggestive that the enzyme induction and thyroid tumors observed in rats may have some relevance to thyroid disorders in humans.

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. (Lumb, Newberne et al. 1978) Noteworthy compared to eplerenone is the absence of findings in the kidney.

One mechanism of action for the thyroid effects of eplerenone in rats is 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 (including eplerenone) and is considered irrelevant to humans. Rats lack thyroid binding globulin and the half-life of circulating thyroxin is substantially shorter than in humans.

COMMENT: Note that spironolactone, like eplerenone, causes reductions in weight of animal prostates. See the last section and the data and discussion of thyroid changes in both the summary of the hypertension NDA and in the HF studies to judge whether induction of UDPGT is irrelevant in humans.

4. Spironolactone Sex Hormone-Related Side Effects

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.

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."

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(Pharmacia 2002) 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. (Huffman, Kampmann et al. 1978)

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. (Jeunemaitre, Chatellier et al. 1987) 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. (Leizorovicz, Guenaneche et al. 1991)

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.

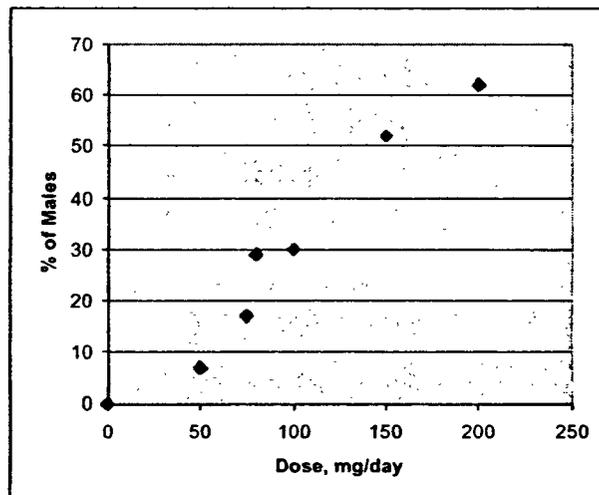


Figure 6: Reviewer's Dose-Response of Spironolactone-Induced Gynecomastia from Published Studies

The RALES trial of spironolactone in heart failure yielded rates of spironolactone-induced gynecomastia consistent with those shown in Figure 2. (Pitt, Zannad et al. 1999) In RALES 822 (603 male) patients received 25-50 mg of spironolactone daily (mean 26

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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). (Jeunemaitre, Chatellier et al. 1987) 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. (Leizorovicz, Guenaneche et al. 1991)

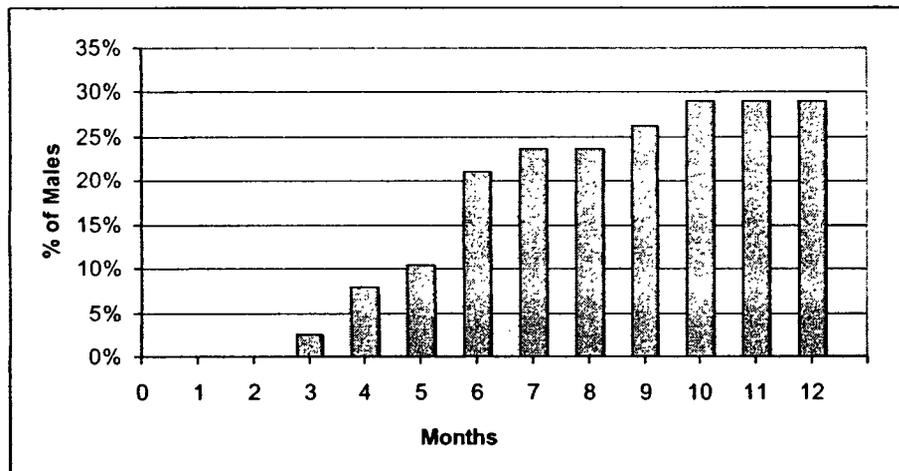


Figure 7: Reviewer's Time to Gynecomastia at Spironolactone 80 mg/day from Leizorovicz et al.

In addition to these reports of sex-hormone related adverse effects of spironolactone, other studies have tried to use spironolactone for treating sex-hormone related disorders, e.g., hirsutism in women and prostatic hypertrophy or carcinoma. One study that appears relevant to this submission involved the treatment of 47 patient having prostatic hypertrophy with spironolactone 100 mg per day for three months. (Zgliczynski, Baranowska et al. 1981) Serum levels of testosterone and dihydrotestosterone fell while progesterone, estradiol, and LH increased. There was a decrease in the size of the prostate glands.

COMMENT: Note that development of gynecomastia appears to be both dose and duration of therapy dependent. From the hypertension studies eplerenone appears to be somewhere between 2-4 times less potent than spironolactone for antihypertensive effects and effects upon RAAS hormones. For EPHEBUS this translates into an equivalent dose

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of spironolactone of about 10-20 mg/day. Even if the relative potency of eplerenone for producing sex hormone-related effects is the same as spironolactone's, one would expect relatively low rates of such adverse effects in EPHESUS.

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%). (Pitt, Zannad et al. 1999) 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. (Schepkens, Vanholder et al. 2001) Two recent articles have also highlighted the association of hyperkalemia with combined spironolactone and ACE inhibitor or angiotensin receptor blocker use. (Anton, Cox et al. 2003; Wrenger, Muller et al. 2003) Butler et al. 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. (Butler, McAvoy et al. 2002)

6. Renin-Angiotensin System and Fibrinolytic Balance

The renin-angiotensin system appears to play a role in fibrinolytic balance. (Vaughan 2002) 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

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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. (Sawathiparnich, Kumar et al. 2002) 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.

COMMENT: 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 hypertension clinical studies and in an EPHEBUS substudy. 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
ANP	atrial natriuretic peptid
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the curve
BB	beta blocker
BID	twice daily

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BP	blood pressure
bpm	beats per minute
BNP	brain natriuretic peptide
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAC	Carcinogenicity Assessment Committee (FDA)
CCB	calcium channel blocker
CEC	Critical Events Committee (for adjudicating endpoints)
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
Coadmin	coadministration
CPK	creatine phosphokinase
CPK-MB	creatine phosphokinase-MB subform
CPN	chronic progressive nephropathy (in rats)
CrCl	creatinine clearance (estimated by Cockcroft-Gault equation)
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
CV	cardiovascular
CYP	cytochrome P-450
DBP	diastolic blood pressure
DSI	Division of Scientific Investigations (FDA)
DSMB	data safety monitoring board
ECG	electrocardiogram
EF	ejection fraction
EPHESUS	<u>E</u> plerenone <u>P</u> ost-AMI <u>H</u> eart Failure <u>E</u> fficacy and <u>S</u> urvival <u>S</u> tudy
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GGT	gamma glutamyl transpeptidase
HCTZ	hydrochlorothiazide
HF	heart failure
HRQOL	health-related quality of life
HRV	heart rate variability
IARC	International Agency for Research on Cancer
ICTP	type I collagen telopeptide
IL-6	interleukin-6
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intention-to-treat
IVRS	interactive voice response system (for randomization)
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOCF	last observation carried forward

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LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVM	left ventricular mass
MCS	Mental Composite Summary (of SF-36)
MI	myocardial infarction
Mono	monotherapy
NDA	New Drug Application
NOAEL	no adverse effect level
nt-ANP	N-terminal atrial natriuretic peptide
NYHA	New York Heart Association
nt-BNP	N-terminal brain natriuretic peptide
PAI-1	plasminogen activator inhibitor-1
PD	pharmacodynamic
PEY	patient exposure years
PIIINP	aminoterminal propeptide of Type III procollagen
PK	pharmacokinetic
PTCR	percutaneous transluminal coronary revascularization
PWV	pulse wave velocity
QD	once daily
QoL	quality of life
QOD	every other day
QTc	QT interval duration corrected for heart rate
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cell count
RALES	Randomized Aldactone Evaluation Study
RD	risk difference
S ₃	third heart sound
SAE	serious adverse event
SAS®	Statistical Analysis System
SF-36	Standard Form-36 (quality of life questionnaire)
SBP	systolic blood pressure
se	seated
SL	spironolactone
sNDA	supplemental NDA
T _{1/2}	half-life
TIA	transient ischemic attack
TIMP	tissue inhibitor of metalloproteinase
T _{max}	time to maximum concentration
TNF-α	tumor necrosis factor-α
t-PA	tissue plasminogen activator
TSH	thyroid stimulating hormone
UACR	urinary albumin:creatinine ratio
ULN	upper limit of normal
US	United States

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

The sponsor did not submit new chemistry or non-clinical pharmacology studies for this sNDA with the exception of some pharmacodynamic studies of possible mechanisms of action in heart failure and some exploratory PK studies. The most clinically relevant findings from other consultant reviews are from the statistical review of this sNDA. The statistical findings are incorporated into the efficacy review. The following summarizes the most-relevant pre-clinical findings from the original NDA submission for hypertension and the pharmacodynamic studies in heart failure.

A. Summary of Animal Toxicity from Original NDA Submission for Hypertension

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

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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

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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).”

COMMENT: Note that eplerenone reduced prostate weights in dogs. The FDA pharmacology review also noted that eplerenone was tested for 5 α -reductase activity in a dog prostate homogenates in Study P3097017. All compounds tested (finasteride, spironolactone, canrenone, and aldosterone) except eplerenone inhibited 5 α -reductase activity in this study. However, the FDA reviewer noted that the sponsor postulated that inhibition of 5 α -reductase activity may still be the mechanism for the prostatic atrophy observed in previous studies.

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 of the original NDA for a detailed description of the findings in the original 2-year rat study, the requested additional studies, and the CAC's evaluation. Also note the summary of spironolactone carcinogenicity in Section I.E.2 above and the more detailed discussion in the medical review of the original NDA for a hypertension indication.

C. Mineralocorticoid Receptor Selectivity

The sponsor's summary of eplerenone mineralocorticoid receptor selectivity is the following:

“The activity of eplerenone at human steroid receptors was measured in vitro using recombinant human steroid receptors. These assays measure the ability of a compound to stimulate the receptor transcriptional transactivation function and/or to antagonize a full agonist transcriptional response at steroid receptors. Eplerenone antagonized human

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mineralocorticoid receptor (hMR) transcriptional activation by aldosterone in a concentration-dependent manner with a calculated IC₅₀ of 291 nM [Report No. BRD01D2128, 7 August 2001]. In an independent assay, eplerenone and spironolactone inhibition of aldosterone-induced hMR activation was concentration-dependent with the potency of eplerenone reduced approximately 40-fold compared to spironolactone [Report No. BRD00D2049, 7 July 2001]. As shown in Figure 2 [not included], eplerenone activity was also reduced at human progesterone (hPR), androgen (hAR) and glucocorticoid (hGR) receptors compared to spironolactone. At 10 μM, eplerenone had no measurable impact on dexamethasone-induced hGR transactivation, whereas spironolactone inhibited the transcriptional response by 20%. Also at 10 μM, eplerenone inhibited only 11% of hAR activation by methyltrienolone compared to 65% for spironolactone. Moreover, eplerenone induced only 5% of the maximum hPR activation compared to 47% with spironolactone. Thus, compared to spironolactone, eplerenone is a more selective aldosterone blocker, with significantly improved MR selectivity relative to GR, AR and PR.”

The following table shows the data from Report No. BRD00D2049 regarding progesterone receptor activity.

Table 2: Sponsor’s Human Progesterone Receptor Activity of Eplerenone and Spironolactone

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

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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 table shows the data from this study regarding androgen receptor activity inhibition.

Table 3: Sponsor's Human Androgen Receptor Activity of Eplerenone and Spironolactone

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

R1881 = methyltrienolone

Note that eplerenone at 10^{-5} M appears to inhibit about 11 percent of androgen receptor activation compared to the 65 percent inhibition observed with spironolactone at the same concentration.

COMMENT: The human receptor inhibition studies are not convincing that the relative potencies of eplerenone and spironolactone are dramatically different for inhibiting the various steroid receptors. While at concentrations of 10^{-5} M eplerenone produced 37-54% less inhibition of androgen and progesterone receptors than spironolactone, eplerenone is also 40-fold less potent than spironolactone at inhibiting the mineralocorticoid receptor. Note also that spironolactone metabolites such as canreno ne are active. To be convincing any in vitro comparisons would have to account for their activities as well as those of the parent drug.

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III. Human Pharmacokinetics, Pharmacodynamics, and Toxicity

A. Pharmacokinetics

For a complete review, see the FDA biopharmaceutics review of the NDA. The material presented here is summarized from the approved label for the hypertension indication, the hypertension NDA, and from the sponsor's summary for the HF indication. It is included here as background to the review of the clinical data contained in this NDA. The clinical reviewer did not analyze the primary data for the following summary.

1. Pertinent Pharmacokinetics from the Hypertension Label

Eplerenone is cleared predominantly by cytochrome P450 3A4 (CYP3A4) metabolism, with an elimination half-life of 4 to 6 hours. No active metabolites of eplerenone have been identified in human plasma. Steady state is reached within 2 days. At steady state, elderly subjects had increases in C_{max} (22%) and AUC (45%) compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19% lower and AUC was 26% lower in blacks. Steady-state C_{max} and AUC were increased by 24% and 38% respectively in patients with severe renal impairment. Steady-state C_{max} and AUC of eplerenone were increased by 36% and 42% respectively in patients with moderate (Child-Pugh Class B) hepatic impairment.

A potent inhibitor of CYP3A4 (ketoconazole) caused increased exposure of about 5-fold while less potent CYP3A4 inhibitors (erythromycin, saquinavir, verapamil, and fluconazole) gave approximately 2-fold increases. Grapefruit juice caused only a small increase (about 25%) in exposure. Eplerenone is not an inhibitor of CYP1A2, CYP3A4, CYP2C19, CYP2C9, or CYP2D6.

No clinically significant drug-drug pharmacokinetic interactions were observed when eplerenone was administered with digoxin, warfarin, midazolam, cisapride, cyclosporine, simvastatin, glyburide, or oral contraceptives. St. Johns Wort (a CYP3A4 inducer) caused a small (about 30%) decrease in eplerenone AUC.

COMMENT:

- The predominant CYP3A4 metabolism suggests that some patients, taking CYP3A4 inhibitors, may experience high exposures. The dosage used in the large HF trial was 25-50 mg, substantially less than the maximum dosage tested in the hypertension trials (400 mg). The typical dose-limited adverse effect has been hyperkalemia, particularly troublesome with daily dosages in excess of 200 mg. Monitoring of serum potassiums was specified in the HF trials with avoidance of