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4.4.1.2.2. Baseline Characteristics by Region

Baseline characteristics varied somewhat by country or region. Selected baseline characteristics by region are shown in the following table.

Table 71: Reviewer's Baseline Characteristics by Region in RALES

	W. Europe	Latin America	US/Canada	Other
N	1066	433	113	50
Patients, %	64%	26%	7%	3%
Mean age	68.3	58.6	64.2	59.8
Male, %	74%	69%	77%	78%
Mean ejection fraction	0.25	0.27	0.21	0.24
Mean pulse	79	85	81	79
Mean SBP	124	120	116	119
Mean DBP	74	77	70	74
NYHA class 3, %	76%	59%	60%	80%
NYHA class 4, %	23%	41%	40%	20%
Ischemic etiology, %	60%	38%	33%	34%
Diabetic, %	25%	12%	34%	14%
Hypertensive, %	27%	8%	48%	28%
History of MI, %	34%	7%	54%	44%
History of stroke, %	6%	2%	11%	2%
History of afib, %	12%	3%	21%	16%

COMMENT: Some of the differences in the table above likely reflect differences in reporting, e.g., the differences between ischemic etiology and history of MI in Western Europe vs. US/Canada. The most relevant comparisons are between the two regions that contributed the vast majority (90%) of the patients, Western Europe and Latin American. The Western European patients are older with more comorbidity than the Latin American patients, but the Western European patients also may have less severe disease and a higher rate of ischemic etiology.

4.4.1.3. Conduct

4.4.1.3.1. Monitoring

Individual patient records were reviewed and verified against the source documents by sponsor clinical personnel in the course of monitoring the clinical investigation. The information on the CRFs was entered into an Oracle database using Recorder via double key verification. All data were checked using a computerized edit system. All values that were outside ranges, invalid, or inconsistent with other data were queried. A 100% audit of the database against CRFs was conducted for all data points. In addition, a 100% audit of the complete database against CRFs was conducted for 10% of the patients. The sponsor's quality assurance group conducted site audits at nine sites.

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4.4.1.3.2. Protocol Changes and Violations

There were minor deviations of the entry criteria. Some examples are the following:

- Three patients (two spironolactone and one placebo) had renal disease at study entry.
- Three patients (one spironolactone and two placebo) had a serum potassium > 5.0 meq/L at the time of first dose.
- Twenty-five patients did not meet all entry criteria for severe HF (16 criteria not met among spironolactone patients and 15 not met among placebo patients.)
- Two spironolactone patients had ejection fractions >35%. The Executive Committee ruled that, if they met the entry criteria at a later date, they could be re-entered. They were subsequently re-entered and the baseline data at the time of re-entry used for the NDA analyses.

Some dosing deviations were noted. Some examples are the following:

- Six patients (four spironolactone and two placebo) were never dosed.
- Three patients (two spironolactone and one placebo) were given another patient's study medication.

4.4.1.3.3. Dosing

4.4.1.3.3.1. Study Drug

A total of 1,658 of the 1,663 randomized patients received at least one dose of study medication: 819 spironolactone patients and 839 placebo patients. The mean daily dose for patients who were receiving study drug at the end of the study was 26 mg in the spironolactone group and 31 mg in the placebo group.

4.4.1.3.3.2. Concomitant Therapy

Other medications taken by the patients at any time during the study are shown in the following table.

Table 72: Sponsor's Concurrent Medications in RALES

Medication Category	Spironolactone (n=822)	Placebo (n=841)
Diuretics	821 (99.9%)	840 (99.9%)
ACE-inhibitors	796 (96.8%)	810 (96.3%)
Other medications	755 (91.8%)	785 (93.3%)
Digoxin	651 (79.2%)	647 (76.9%)
Anticoagulants	472 (57.4%)	504 (59.9%)
Aspirin	355 (43.2%)	365 (43.4%)
Potassium supplements	296 (36.0%)	359 (42.7%)
Beta blockers	126 (15.3%)	122 (14.5%)
Calcium channel blockers	118 (14.4%)	116 (13.8%)

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COMMENT: The medications use is well-balanced between the two groups except for the greater use of potassium supplements in the placebo group. Note that the rates of use of beta blockers is low by current recommendations.

4.4.2. Efficacy

4.4.2.1. Primary Endpoint

More placebo patients (386, 46%) died during the study compared to spironolactone patients (284, 35%). The difference in survival times is highly statistically significant by the log-rank test ($p < 0.001$). The Kaplan-Meier survival curves are shown in the following figure.

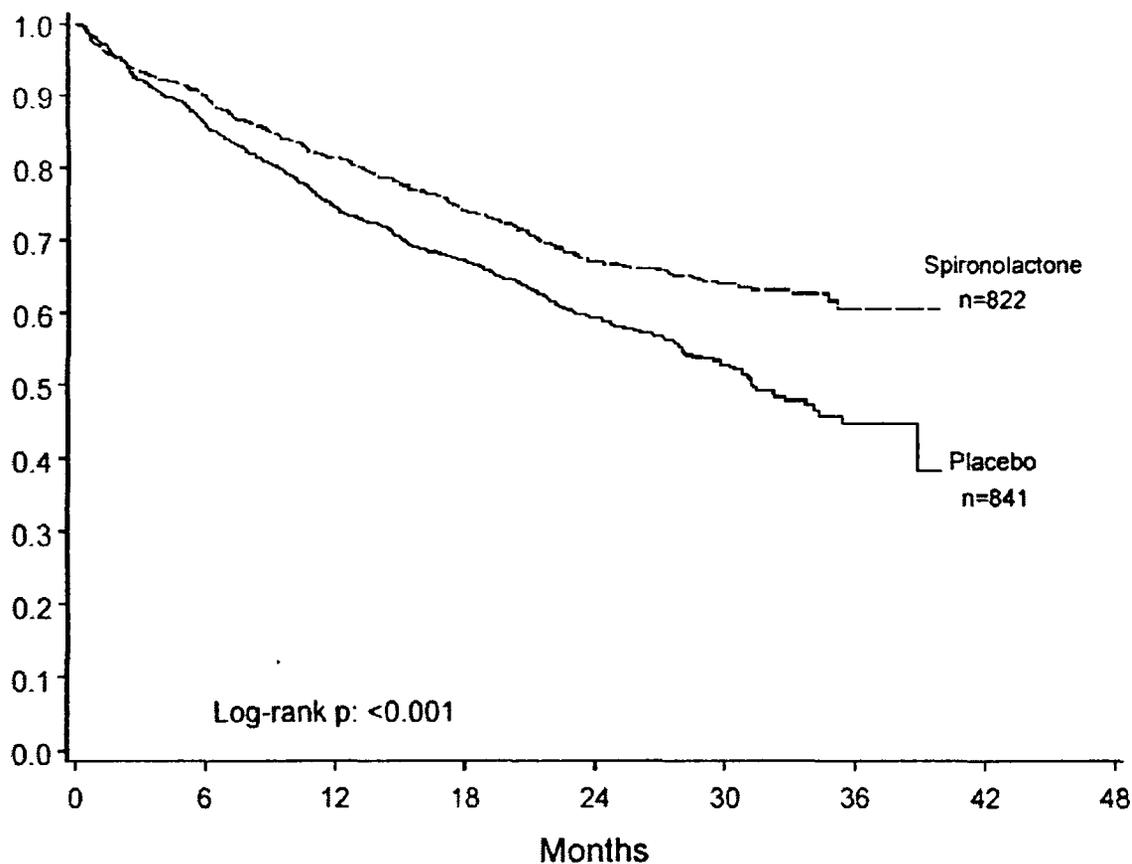


Figure 9: Sponsor's Kaplan-Meier Survival Plots for RALES

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For all patients, the addition of spironolactone to standard therapy reduced the risk of death by 30% compared to placebo ($p < 0.001$; 95% CI 0.18, 0.40).

Patients (1374 placebo and 1361 eplerenone) with potassium levels < 5.0 meq/L and serum creatinines < 2.5 mg/dL continued to receive blinded study medication in an extension study until the database was unblinded. A total of 44 patients died during the treatment extension or within 30 days of the last dose of study medication, 21 in the placebo group and 23 in the eplerenone.

COMMENT: Note that the curves do not start to diverge until about three months. The divergence of the curves is impressive.

4.4.2.2. Secondary Endpoints

4.4.2.2.1. Cardiac Mortality

Cardiac mortality (defined as sudden cardiac death, MI, or progressive HF) was also highly statistically significantly reduced by spironolactone. Mortality by cause in RALES is shown in the following table.

Table 73: Sponsor's Mortality by Cause in RALES

	Spironolactone (n=822)	Placebo (n=841)	Total (n=1663)
TOTAL MORTALITY*	284 (34.5%)	386 (45.9%)	670 (40.3%)
<i>Cardiac Mortality*</i>	226 (27.5%)	314 (37.3%)	540 (32.5%)
Sudden Cardiac Death	82 (10.0%)	110 (13.1%)	192 (11.5%)
Myocardial Infarction	17 (2.1%)	15 (1.8%)	32 (1.9%)
Progression of CHF	127 (15.5%)	189 (22.5%)	316 (19.0%)
<i>Other Mortality</i>	58 (7.1%)	72 (8.6%)	130 (7.8%)
Stroke	8 (1.0%)	11 (1.3%)	19 (1.1%)
Other Cardiovascular Death	12 (1.5%)	13 (1.5%)	25 (1.5%)
Noncardiovascular Death	29 (3.5%)	41 (4.9%)	70 (4.2%)
Unknown	9 (1.1%)	7 (0.8%)	16 (1.0%)

* Log-rank p-value for total mortality $p < 0.001$. Log-rank p-value for cardiac mortality $p < 0.001$.

COMMENT: Note that deaths due to progression of HF were significantly lower with spironolactone and sudden cardiac death was also lower with spironolactone.

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4.4.2.2.2. Cardiac Hospitalization and Combined Cardiac Mortality/Hospitalization

Rates of non-fatal hospitalizations overall and by cardiac cause are shown in the following table.

Table 74: Sponsor's Rates of Non-Fatal Hospitalizations in RALES

	Spironolactone (n=822)		Placebo (n=841)		Total (n=1663)	
Total Non-Fatal Hospitalizations	421 (51.2%)	1060	481 (57.2%)	1317	902 (54.2%)	2377
HF Aggravation (definitive)	209 (25.4%)	391	289 (34.4%)	624	498 (29.9%)	1015
HF Aggravation (non-specific)	18 (2.2%)	22	34 (4.0%)	39	52 (3.1%)	61
Atrial Flutter/Fibrillation or Supraventricular Tachycardia	30 (3.6%)	40	23 (2.7%)	39	53 (3.2%)	79
Ventricular Arrhythmias	23 (2.8%)	25	24 (2.9%)	31	47 (2.8%)	56
Myocardial Infarction	10 (1.2%)	11	14 (1.7%)	15	24 (1.4%)	26
Angina (stable or unstable)	43 (5.2%)	66	35 (4.2%)	44	78 (4.7%)	110
Stroke	14 (1.7%)	15	20 (2.4%)	24	34 (2.0%)	39
Other Cardiovascular	91 (11.1%)	129	93 (11.1%)	124	184 (11.1%)	253
Non-Cardiovascular	223 (27.1%)	361	232 (27.6%)	377	455 (27.4%)	738

Time to first non-fatal hospitalization was significantly longer in the spironolactone group ($p = 0.0005$ by logrank test). The point estimates of hospitalization rates are better for spironolactone for most categories except atrial arrhythmias and angina. However, the only category that is dramatically better for spironolactone is HF aggravation.

For secondary endpoints cardiac hospitalization was defined in the original protocol as hospitalization defined as hospitalization for HF aggravation, atrial flutter/ fibrillation or supraventricular tachycardia, ventricular arrhythmias, angina, MI, or stroke. The NDA presents data on cardiac hospitalizations defined as HF aggravation, ventricular arrhythmia, MI, or angina. For the latter definition, more placebo patients (40%) were hospitalized for non-fatal cardiac events than spironolactone patients (32%, log-rank $p < 0.001$).

4.4.2.2.3. NYHA Class

Changes in NYHA class were more favorable with spironolactone than placebo as shown in the following table.

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Table 75: Sponsor's Changes in NYHA Class in RALES

	Spironolactone (n=822)	Placebo (n=841)	Total (n=1663)	P-value
Baseline NYHA Class III				
N with change	586	575	1161	
Final NYHA				0.001
I	51 (8.7%)	33 (5.7%)	84 (7.2%)	
II	180 (30.7%)	154 (26.8%)	334 (28.8%)	
III	148 (25.3%)	134 (23.3%)	282 (24.3%)	
IV	21 (3.6%)	14 (2.4%)	35 (3.0%)	
Death	186 (31.7%)	240 (41.7%)	426 (36.7%)	
Worsening	207 (35.3%)	254 (44.2%)	461 (39.7%)	0.002
No change	148 (25.3%)	134 (23.3%)	282 (24.3%)	
Improvement	231 (39.4%)	187 (32.5%)	418 (36.0%)	
Baseline NYHA Class IV				
N with change	223	254	477	
Final NYHA				0.003
I	18 (8.1%)	9 (3.5%)	27 (5.7%)	
II	41 (18.4%)	38 (15.0%)	79 (16.6%)	
III	45 (20.2%)	43 (16.9%)	88 (18.4%)	
IV	21 (9.4%)	19 (7.5%)	40 (8.4%)	
Death	98 (43.9%)	145 (57.1%)	243 (50.9%)	
Worsening	98 (43.9%)	145 (57.1%)	243 (50.9%)	0.005
No change	21 (9.4%)	19 (7.5%)	40 (8.4%)	
Improvement	104 (46.6%)	90 (35.4%)	194 (40.7%)	

Baseline health-related Quality of Life (HRQOL) was assessed in a subsample of 88 patients in two participating countries, Brazil and Canada. Sixty patients had complete data for the six months of follow-up. The sponsor's summary of the changes is as follows:

"At Months 3 and 6 there were statistically significant and clinically meaningful changes from baseline for all eight SF-36 dimension scores in the spironolactone group, compared to only six dimensions in the placebo group (Table 36.3 [not included in this review]). At Month 3, the spironolactone group had statistically significantly greater improvements in Mental Health ($p=0.004$) and Mental Composite Summary (MCS) ($p=0.016$) subscale scores compared to placebo.

"The positive impact of spironolactone treatment on change from baseline for Mental Health subscale scores continued to be statistically significant and clinically important at

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six months ($p=0.044$). The trend toward beneficial effects on overall MCS was still apparent, but the difference between treatment groups was not statistically significant ($p=0.418$).”

COMMENT: The small, non-representative sample size and the short evaluation period make these data difficult to interpret.

4.4.2.3. Subgroup Analyses

4.4.2.3.1. Region and Country

4.4.2.3.1.1. Mortality by Region and Country

Mortality rates were lower with spironolactone in all regions as shown in the following table.

Table 76: Reviewer’s Mortality Rates by Region in RALES

	Placebo	Spironolactone
Latin America	45%	32%
Rest of world	42%	38%
US/Canada	47%	41%
US	42%	38%
Canada	50%	44%
Western Europe	46%	35%

The benefit of spironolactone compare to placebo regarding mortality reduction appears to be less in the US and Canada. However, the numbers of patients enrolled in the US and Canada is low such that the confidence intervals for the mortality estimates are wide (33-60% for placebo, 28-55% for spironolactone in US/Canada).

4.4.2.3.1.2. Hospitalizations by Region and Country

The percentages of patients hospitalized and not dying in hospital were lowest in Latin America as shown in the following table.

Table 77: Reviewer’s Percentages of Patients Hospitalized at Least Once and Not Dying In Hospital by Region in RALES

	Placebo	Spironolactone
Latin America	35%	30%
Rest of world	54%	58%
US/Canada	60%	66%
US	57%	88%

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	Placebo	Spironolactone
Canada	63%	50%
Western Europe	66%	58%

While the hospitalization rates appear to be higher in US and the rest of the world with spironolactone, the numbers of cases in these areas are low and the confidence intervals of the rates are wide.

4.4.2.3.2. Race

The numbers of non-white patients enrolled in RALES are too small to document any efficacy differences by race. The mortality results by race are shown in the following table.

Table 78: Reviewer's Mortality Rates by Race in RALES

	Placebo	Spironolactone
Asian	53%	47%
Black	42%	39%
Other	34%	31%
White	47%	34%

4.4.2.3.3. Age and Gender

Mortality was lower for all age categories with spironolactone, although the benefit appears to be reduced for younger ages as shown in the following table.

Table 79: Reviewer's Mortality Rates by Age Category in RALES

	Placebo	Spironolactone
<55	30%	29%
55-64	42%	31%
65-74	49%	35%
≥75	59%	41%

Nonfatal hospitalization rates were substantially lower with spironolactone for all age groups except for age ≥ 75, for which they were similar (spironolactone 59%, placebo 60%).

Mortality rates were higher in males despite a lower mean age in males. Mortality rates were comparably lower with spironolactone in both genders as shown in the following table.

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Table 80: Reviewer's Mortality Rates by Gender in RALES

	Placebo	Spironolactone
Female	42%	31%
Male	47%	36%

Nonfatal hospitalization rates were lower with spironolactone for both genders.

4.4.2.3.4. Other Subgroups

I examined the following other baseline factors for their relationships to mortality and spironolactone treatment:

- Spironolactone was associated with reduced mortality for both NYHA class 3 and class 4 HF as shown in the following table.

Table 81: Reviewer's Mortality Rates by NYHA Class in RALES

NYHA Class	Placebo	Spironolactone
3	41%	31%
4	56%	43%

- Spironolactone was associated with reduced mortality for patients with a history of diabetes and those without. A history of diabetes was associated with increased mortality.
- Spironolactone was associated with reduced mortality for all levels of baseline renal function. The mortality rates were high in patients with severe renal impairment at baseline (creatinine clearance ≤ 30 ml/min) but they were substantially lower with spironolactone (59% vs. 73%).
- Spironolactone was associated with reduced mortality for patients with a history of hypertension and those without. The benefit appears to be slightly less in patients with a history of hypertension as shown in the following table.

Table 82: Reviewer's Mortality Rates by History of Hypertension in RALES

Hx of hypertension	Placebo	Spironolactone
No	47%	34%
Yes	44%	38%

- Spironolactone was associated with reduced mortality for all baseline SBP levels except SBP ≤ 90 mm Hg. Mortality decreased with increasing baseline BP except perhaps for SBP > 150 as shown in the following table.

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Table 83: Reviewer's Mortality Rates by Baseline SBP in RALES

Baseline SBP	Placebo	Spironolactone
≤90	68%	68%
91-100	55%	39%
101-110	51%	43%
111-120	44%	32%
121-130	39%	28%
131-140	39%	25%
141-150	36%	32%
>150	42%	23%

- Spironolactone was associated with reduced mortality regardless of the presumed etiology of the HF (ischemic vs. nonischemic) or history of MI.
- CV mortality increased with decreasing baseline potassium levels with placebo but was relatively constant across varying baseline potassium levels with spironolactone, as shown in the following table.

Table 84: Reviewer's CV Mortality Rates by Baseline Potassium in RALES

Baseline potassium	Placebo	Spironolactone
≤3.3	64%	30%
3.31-3.5	52%	30%
3.51-3.7	43%	33%
3.71-3.9	44%	35%
3.91-4.1	38%	30%
4.11-4.5	39%	27%
4.51-5	39%	33%
>5	33%	27%

COMMENT: All but one of these subgroup analyses do not suggest any remarkable variations regarding the effects of spironolactone. They are compared to the eplerenone subgroup analyses in the Integrated Review of Efficacy. The interesting subgroup analysis is that regarding CV mortality and baseline potassium. Spironolactone appears to have greater benefit with lower baseline potassium levels.

4.4.2.3.5. Interactions with Other CV Drugs

RALES is an older study, so concomitant medication use does not reflect current standards of practice. All patients were supposed to be on a loop diuretic and an ACE inhibitor (if tolerated). However less than 10% of patients were treated with beta

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blockers at baseline. The differences in mortality by baseline beta blocker use are striking as shown in the following table.

Table 85: Reviewer's CV Mortality by Baseline Beta Blocker Use in RALES

Beta blocker	Placebo	Spironolactone
no	41%	32%
yes	33%	11%

The differences in CV mortality by any beta blocker use are similar for no beta blocker use but less pronounced for any beta blocker use (placebo 29% vs. spironolactone 16%).

Because loop diuretic and ACE inhibitor use was an inclusion criterion and ARB use was rare, the only other CV medication use worth noting in RALES was digitalis use. CV mortality with spironolactone was lower regardless of any digitalis use as shown in the following table.

Table 86: Reviewer's CV Mortality by Any Digitalis Use in RALES

Digitalis	Placebo	Spironolactone
no	32%	26%
yes	43%	31%

The age differentials for baseline CV medication in RALES were the opposite of those seen in EPHEBUS as shown in the following table.

Table 87: Reviewer's Mean Ages of Patients by Baseline CV Medication Use in RALES

Baseline Use	No	Yes
Beta blocker	65	68
Aspirin	64	67
Digitalis	68	64

COMMENT: The effects relative to beta blocker and digitalis use in RALES are similar to those in EPHEBUS but less pronounced. Both spironolactone and eplerenone are more effective in patients taking beta blockers and digitalis. What might be the mechanism for this difference is difficult to estimate.

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4.4.3. Safety

4.4.3.1. Exposure

A total of 1,658 of the 1,663 randomized patients received at least one dose of study medication: 819 spironolactone patients and 839 placebo patients. For spironolactone this represents over 1,300 patient exposure years. The mean daily dose for patients who were receiving study drug at the end of the study was 26 mg in the spironolactone group and 31 mg in the placebo group.

4.4.3.2. Serious Adverse Events

4.4.3.2.1. Deaths

All cause mortality was the primary endpoint in RALES. The mortality results, including CV mortality causes, are presented in Section 4.4.2 above. Other causes of death were similar between the two groups, although there were nine deaths from cancer in the spironolactone group and six in the placebo group.

4.4.3.2.2. Hospitalizations

Hospitalizations were a secondary endpoint in RALES. Hospitalization rates are discussed in Section 4.4.2.2 above.

4.4.3.2.3. Other serious adverse events

Serious adverse events occurred in 66% of spironolactone patients and 75% of placebo patients. SAEs that occurred in 2% or more of patients in either group are shown in the following table.

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Table 88: Sponsor's SAEs with Rates \geq 2% in RALES

Body System Adverse Event	Spironolactone (n=822)**	Placebo (n=841)*	p-Value
General Cardiovascular	337 (41.0%)	445 (52.9%)	0.086
Cardiac failure	307 (37.3%)	419 (49.8%)	
Left cardiac failure	41 (5.0%)	49 (5.8%)	
Unstable angina	20 (2.4%)	15 (1.8%)	
Body as a Whole	161 (19.6%)	181(21.5%)	0.600
Sudden death	91 (11.1%)	117 (13.9%)	
Chest pain	28 (3.4%)	29 (3.4%)	
Heart & Rhythm	96 (11.7%)	98 (11.7%)	0.294
Atrial fibrillation	23 (2.8%)	22 (2.6%)	
Ventricular tachycardia	20 (2.4%)	16 (1.9%)	
Ventricular fibrillation	13 (1.6%)	21 (2.5%)	
Respiratory	82 (10.0%)	109 (13.0%)	0.451
Bronchitis	33 (4.0%)	42 (5.0%)	
Pneumonia	30 (3.6%)	47 (5.6%)	
Metabolic & Nutritional	80 (9.7%)	76 (9.0%)	0.159
Hyperkalemia	22 (2.7%)	15 (1.8%)	
Aggravated diabetes mellitus	12 (1.5%)	18 (2.1%)	
Myocardial, Endocardial, Pericardial & Valve	57 (6.9%)	77 (9.2%)	0.477
Angina pectoris	28 (3.4%)	30(3.6%)	
Myocardial infarction	25 (3.0%)	43 (5.1%)	
Extracardiac Vascular	56 (6.8%)	56 (6.7%)	0.383
Cerebrovascular disorder	24 (2.9%)	27 (3.2%)	
Peripheral ischemia	23 (2.8%)	19 (2.3%)	
Gastrointestinal	55 (6.7%)	66 (7.8%)	1.000
Autonomic Nervous	42 (5.1%)	33 (3.9%)	0.078
Syncope	28 (3.4%)	19 (2.3%)	
Resistance Mechanism	29 (3.5%)	54 (6.4%)	0.056
Infection	17 (2.1%)	28 (3.3%)	
Urinary	28 (3.4%)	46 (5.5%)	0.193
UTI	9 (1.1%)	18 (2.1%)	
Platelet, Bleeding & Clotting	25 (3.0%)	30 (3.6%)	1.000
Neoplasm	21 (2.6%)	16 (1.9%)	0.187
Red Blood Cell	17 (2.1%)	12 (1.4%)	0.190
Psychiatric	16 (1.9%)	17 (2.0%)	0.861
Musculoskeletal	15 (1.8%)	18 (2.1%)	1.000

COMMENT: Note that the lower rate of SAEs with spironolactone is predominantly the result of the lower rate of HF with it.

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4.4.3.3. Events Leading to Discontinuation

Eighty-nine (11%) patients in the spironolactone group and 96 (11%) patients in the placebo group discontinued study medication because of at least one adverse event. The AEs leading to discontinuation in more than one spironolactone patient are shown in the following table:

Table 89: Reviewer's Events Leading to Discontinuation in RALES

	Placebo		Spironolactone	
	N	%	N	%
Treated patients	839		819	
Sudden death	28	3.3%	13	1.6%
Hyperkalemia	3	0.4%	9	1.1%
Creatinine increased	1	0.1%	7	0.9%
Gynecomastia	3	0.4%	8	1.0%
Nausea	3	0.4%	5	0.6%
Arrhythmia	4	0.5%	5	0.6%
Acute renal failure	2	0.2%	5	0.6%
Depression/paranoia	0	0.0%	4	0.5%
Cardiac failure	13	1.5%	4	0.5%
Cardiac arrest	6	0.7%	3	0.4%
Emergent surgery	2	0.2%	3	0.4%
Myocardial infarction	1	0.1%	3	0.4%
Hyponatremia	0	0.0%	3	0.4%
Pain	0	0.0%	3	0.4%
Headache	1	0.1%	2	0.2%
Hypotension	1	0.1%	2	0.2%

COMMENT: Note that sudden death and cardiac failure were more frequent causes for withdrawal with placebo while hyperkalemia, gynecomastia, and creatinine increased or acute renal failure were more frequent with spironolactone.

4.4.3.4. Laboratory Test Value Changes

Lab tests in RALES were limited to sodium, potassium, and creatinine for the whole population. Atrial natriuretic peptide was measured in a subset of patients.

The mean serum potassium level at baseline was 4.27 mmol/L in the placebo group and 4.27 mmol/L in the spironolactone group. Mean potassium increased by 0.03 in the placebo group and 0.27 in the spironolactone group by the last visit ($p < 0.001$). More spironolactone-treated patients had extreme potassium values (defined as potassium > 5.5 mmol/L) compared to placebo-treated patients for the final visit (3.9% vs 1.6%, $p = 0.006$) and maximum value (15.5% vs 4.5%, $p < 0.001$). Because virtually all patients

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were on ACE inhibitors, comparisons of potassium levels with and without ACE inhibitor use is not possible in RALES.

The mean creatinine level at baseline was 1.25 mg/dL in the placebo group and 1.24 mg/dL in the spironolactone group. Mean creatinine increased by 0.14 in the placebo group and 0.21 in the spironolactone group by the last visit ($p=0.0017$). Creatinine changes did not vary significantly by gender.

4.4.3.5. Vital Sign Changes

For pulse, a mean decrease from baseline was seen at most visits in both treatment groups. In the spironolactone group, the mean pulse at baseline was 80.7 bpm and mean decreases at subsequent visits ranged from -0.5 bpm to -5.8 bpm. In the placebo group, the mean pulse at baseline was 81.0 bpm and mean changes at subsequent visits ranged from 0.5 bpm to -4.1 bpm. In general, mean decreases in both treatment groups were more pronounced as time progressed. There were no statistically significant differences between treatment groups in change in pulse from baseline at any time.

In the spironolactone group, mean decreases from baseline SBP were seen throughout the study. At baseline, mean SBP was 122.8 mmHg and mean decreases at subsequent visits ranged from -0.7 mmHg to -4.9 mmHg; mean decreases were more pronounced as time progressed. In the placebo group, mean increases from baseline in SBP were seen throughout the study except at month 42. At baseline, mean SBP was 121.6 mmHg and mean increases at subsequent visits ranged from 0.2 mmHg to 2.4 mmHg; in general, mean increases were more pronounced as time progressed. There were statistically significant differences between treatment groups in mean change from baseline in SBP at weeks 4 and 12 and at months 6 and 36; at each of these timepoints, the placebo group had a mean increase from baseline and the spironolactone group had a mean decrease from baseline.

In the spironolactone group, mean decreases from baseline DBP were evident from the first post-baseline visit (week 4) and throughout the study. Mean DBP at baseline was 74.7 mmHg and mean decreases at subsequent visits ranged from -0.6 mmHg to -2.5 mmHg. Decreases were more pronounced as time progressed. In the placebo group, mean decreases from baseline in DBP became evident after approximately six months of treatment. Mean DBP at baseline was 74.5 mmHg, and mean changes at subsequent visits varied between 0.4 mmHg ($n=22$) and -1.2 mmHg. Between months 6 and 36, mean decreases from baseline were generally progressively greater. Patients receiving spironolactone experienced decreases in DBP more quickly after the initiation of therapy than those receiving placebo. Over the course of the study, these decreases were more pronounced in the spironolactone group. There were statistically significant differences between treatment groups in mean change from baseline in diastolic BP at weeks 8 and 12; at both of these timepoints, the placebo group had a mean increase or no change from baseline and the spironolactone group had a mean decrease from baseline.

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COMMENT: The spironolactone group had slightly lower BP in this study, with differences of about 2 mm Hg for SBP and 1 mm Hg for DBP. How these BP changes contributed to or resulted from events during the trial is difficult to interpret.

4.4.3.6. Events of Special Interest

4.4.3.6.1. Hyperkalemia and Hypokalemia

Hyperkalemia was reported as an AE for 83 (10%) spironolactone patients and 30 (4%) placebo patients. Hyperkalemia was reported as an SAE for 22 (3%) spironolactone patients and 15 (2%) placebo patients. Hyperkalemia resulting in discontinuation of study medication occurred in nine (1.1%) spironolactone patients and in three (0.4%) placebo patients. One patient (placebo group) died from hyperkalemia. Thirty-six (4%) spironolactone patients and 11 (1%) placebo patients had valid serum potassium levels \geq 6.0 mmol/L.

Hypokalemia was reported as an AE for 13 (2%) spironolactone patients and 32 (4%) placebo patients. Hypokalemia was reported as an SAE for 3 (0.4%) spironolactone patients and no placebo patients.

Elevated potassium levels were more frequent with reduced baseline renal function as shown in the following table.

Table 90: Reviewer's Mean Changes in Potassium Levels by Baseline Creatinine Clearance in RALES

CrCl	Placebo	Spironolactone
≤ 30	0.32	0.42
31-50	0.01	0.26
51-70	0.01	0.29
71-100	0.01	0.23
>100	-0.03	0.24

CrCl = baseline creatinine clearance, ml/min
(potassium changes mmol/L)

Hyperkalemia SAEs were reported more frequently with spironolactone for lower baseline renal function as shown in the following table.

Table 91: Reviewer's Patients with Hyperkalemia SAEs by Baseline Creatinine Clearance in RALES

CrCl	Placebo	Spironolactone
≤ 30	2.0%	7.8%
31-50	2.3%	4.2%

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CrCl	Placebo	Spirolactone
51-70	2.3%	1.8%
71-100	1.0%	1.7%
>100	0.0%	0.0%

COMMENT: Urine protein was not measured in RALES. Unfortunately, one can not determine whether spironolactone produces more hyperkalemia in diabetic patients with proteinuria as eplerenone appears to do.

4.4.3.6.2. Sex Hormone-Related Adverse Events

Among males, 55 (9%) spironolactone patients and 7 (1%) of placebo patients developed gynecomastia. The median time to development of gynecomastia in the spironolactone group was 677 days, with an interquartile range of 400 to 867 days. Gynecomastia resulted in discontinuation of study drug in six (1%) spironolactone patients and one (0.2%) placebo patient. The rates of male breast pain were 1.7% in the spironolactone group and 0.2% in the placebo group. Two (0.3%) spironolactone patients and one (0.2%) placebo patient stopped study treatment because of male breast pain. Impotence was reported by 0.2% of spironolactone patients and 0.7% of placebo patients. Impotence resulted in cessation of study drug in one (0.2%) spironolactone patient and in one (0.2%) placebo patient. Decrease in libido was not reported as an AE in either treatment group.

Among females, one (0.5%) spironolactone patient and no placebo patients reported an AE of breast pain. One (0.5%) spironolactone patient and no placebo patients reported an AE of menstrual disorder.

COMMENT: Note the long median time to development of gynecomastia.

4.4.3.6.3. Neoplasms

Cancers and other neoplasms were uncommon enough in RALES to make inferences difficult. For ease of comparison the table below is identical in format to that for EPHESUS in Section 3.4.3.6.3.

Table 92: Reviewer's Patients with Cancers or Neoplasms in RALES

	Placebo		Spirolactone	
	N	%	N	%
Patients	841		822	
All cancers*	19	2.3%	21	2.6%
Neoplasms#	0	0.0%	1	0.1%
Lung cancer	4	0.5%	7	0.9%
Gastrointestinal cancer	5	0.6%	8	1.0%

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	Placebo		Spironolactone	
	N	%	N	%
Esophageal cancer	2	0.2%	1	0.1%
Bladder cancer	2	0.2%	2	0.1%
Renal cancer	1	0.1%	0	0.0%
Renal mass	0	0.0%	0	0.0%
Adrenal adenoma	0	0.0%	0	0.0%
Thyroid cancer	0	0.0%	0	0.0%
Females	227		219	
Breast cancer	1	0.4%	1	0.5%
Cervical cancer	0	0.0%	0	0.0%
Ovarian cancer	0	0.0%	0	0.0%
Vulvar/vaginal cancer	0	0.0%	0	0.0%
Males	614		603	
Prostate cancer	2	0.4%	2	0.4%
Benign prostatic hypertrophy	9	1.5%	10	1.7%

* Except non-melanoma skin cancers (One spironolactone patient had both a prostate adenocarcinoma and a B-cell non-Hodgkins's lymphoma of the left knee.)

Neoplasms = tumors not identified clearly as benign or malignant or site

COMMENT: The data files regarding SAEs provided with the original sNDA submission were incomplete and the coding of cancers and neoplasms was erratic. In the original sNDA submission data files only 15 patients were coded as having any carcinoma (except skin) or a malignant neoplasm and 1 additional was coded as having a "neoplasm". Text Table 11 in the RALES study report, however, lists 37 neoplasms that were SAEs. The sponsor confirmed that the data files in the original sNDA submission were incomplete for SAEs.

I requested and obtained "Drug Experience Reports" (DERs) that the sponsor claims are the complete record of SAEs in RALES. I coded both the DERs and the data files in the original sNDA to produce the preceding table. From these DERs I confirmed the two cases of breast and prostate cancers each included in the table above. In addition, I identified two additional cases of prostate cancer, one in each treatment group. One was described as a prostatic epithelioma and coded as a prostatic disorder but a note on the DER states that malignancy of the prostatic epithelioma was confirmed. Another was in a patient started on placebo in November 1995 with no GU problems noted on the baseline history and with DER reports not mentioning prostate cancer in December 1995 (at which time placebo was stopped) but another DER report noting prostate cancer in April 1998. These reports illustrate that prostate cancer may be underreported in RALES and that AE reporting is not highly reliable. It is not reassuring that the original sNDA submission data files code 16 cancers or neoplasms, the study reports counts 37 neoplasms, and I found 40 cancers or neoplasms.

4.4.3.6.4. Thyroid Disorders

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Rates of some thyroid disorders differed between the two groups as shown in the following table.

Table 93: Reviewer's Patients with Thyroid Adverse Events in RALES

	Placebo		Spironolactone	
	N	%	N	%
Patients	841		822	
Hyperthyroidism	4	0.5%	8	1.0%
Hypothyroidism	10	1.2%	15	1.8%
Goiter	1	0.1%	1	0.1%
Thyroid cancer	0	0.0%	0	0.0%

COMMENT: Note that both hyperthyroidism and hypothyroidism are slightly more frequent in the spironolactone group similar to the increased rates in the eplerenone group in EPHEBUS.

4.4.3.6.5. Thrombotic Events

Thrombotic events did not differ significantly between the two groups, as shown in the following table.

Table 94: Reviewer's Patients with Thrombotic Adverse Events in RALES

	Placebo		Spironolactone	
	N	%	N	%
Patients	841		822	
Myocardial infarction	43	5.1%	25	3.0%
Stroke/TIA	27	3.2%	24	2.9%
Arterial thromboses	5	0.6%	6	0.7%
Thrombophlebitis	5	0.6%	4	0.5%
Pulmonary embolism	5	0.6%	5	0.6%

4.4.3.7. Overall Adverse Events

Treatment-emergent adverse events were experienced by 74% of patients in the placebo group and 77% of patients in the spironolactone group. All significant differences in AE rates between eplerenone and placebo have been commented upon in the previous sections.

4.5. Summary

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4.5.1. Efficacy Summary

In RALES spironolactone reduced the risk of death by 30% compared to placebo in patients with NYHA class III-IV HF ($p < 0.001$). While the study had few U.S. participants and the follow-up rate was less than ideal, it supports the concept that an aldosterone blocker can improve survival in HF patients.

Spironolactone reduced mortality from both sudden death and from progression of HF. The major contributor was reduction in deaths from HF rather than sudden death. Non-CV deaths were also lower in the spironolactone group, highlighting the problems in interpreting differences in causes of death.

Spironolactone showed improved survival in all regions, races (although whites predominated), both genders, both NYHA class 3 and 4, and ischemic and nonischemic etiology. Subgroup variations of interest are the following:

- Mortality was lower with spironolactone for all age categories, although the benefit appears reduced for younger ages. The elderly = 75 had a good mortality benefit (41% vs. 59%).
- Mortality was lower with spironolactone in diabetics. Proteinuria was not measured in RALES.
- Spironolactone was associated with reduced mortality for all levels of baseline renal function. The mortality rates were high in patients with severe renal impairment at baseline (creatinine clearance ≤ 30 ml/min) but they were substantially lower with spironolactone (59% vs. 73%).
- Spironolactone was associated with reduced mortality for patients with a history of hypertension and those without. The benefit appears to be slightly less in patients with a history of hypertension (38% vs. 44%) than in those without a history of hypertension (34% vs. 47%).
- CV mortality increased with decreasing baseline potassium levels with placebo but was relatively constant across varying baseline potassium levels with spironolactone (see Table 84).

In RALES use of a loop diuretic and ACE inhibitor were eligibility requirements, so the most pertinent other CV drug uses are regarding beta blockers and digitalis: CV mortality was dramatically lower with combined spironolactone and beta blocker use (see Table 85). Mortality with spironolactone was lower regardless of digitalis use. In RALES beta blocker users had a higher mean age while digitalis users had a lower mean age.

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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.

4.5.2. Safety Summary

RALES represents over 1,300 patient exposure years to spironolactone. The mean dose was 26 mg. Overall AEs were slightly more frequent with spironolactone (77% of patients) than with placebo (74%). SAEs were less frequent with spironolactone (66% of patients) than with placebo (75%). The lower rate of SAEs with spironolactone is predominantly the result of the lower rate of HF with it. The noteworthy AEs related to spironolactone in RALES are the following:

- Hyperkalemia was more frequent with spironolactone. More spironolactone-treated patients had extreme potassium values (defined as potassium >5.5 mmol/L) compared to placebo-treated patients for the final visit (3.9% vs. 1.6) and maximum value (15.5% vs. 4.5). Hyperkalemia was reported as an AE for 83 (10%) spironolactone patients and 30 (4%) placebo patients. Hyperkalemia was more frequent as baseline renal function decreased particularly with spironolactone.
- Hypokalemia was less frequent with spironolactone. Hypokalemia AEs were reported in 2% of spironolactone patients and in 4% of placebo patients.
- Among males, 9% of spironolactone patients and 1% of placebo patients developed gynecomastia. The median time to development of gynecomastia in the spironolactone group was 677 days.
- Both hyperthyroidism (1.0% vs 0.5%) and hypothyroidism (1.8% vs. 1.2%) AEs were slightly more frequent with spironolactone treatment than with placebo.
- Prostate cancers (two each) and breast cancers (one each) were evenly distributed between the two treatment groups.

All of these safety data must be viewed in the light that the reporting and coding of AEs appears to have been somewhat unreliable.

4.5.3. Conclusions

RALES demonstrates reasonably that spironolactone reduces mortality (30% risk reduction) in NYHA class III-IV HF patients treated with loop diuretics and ACE inhibitors. The benefit may be greater in patients treated additionally with beta blockers. The risk of hyperkalemia is tolerable. The one AE that may be troublesome is

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gynecomastia. How the RALES efficacy results compare to EPHEBUS is addressed in the next section.

D. Efficacy Conclusions

This sNDA includes one pivotal study, EPHEBUS, supporting the new indication for HF post-MI. Hence the efficacy conclusions for it are those in the Efficacy Summary for EPHEBUS, Section 3.5.1. The major questions not addressed there are whether one trial alone is sufficient to support the new indication and what is the relevance of RALES.

EPHEBUS showed a mortality risk reduction of about 15% with a p value of 0.008. There are no major challenges to the validity of these results. Given the vital benefit and a reasonable p value, EPHEBUS alone is adequate to support approval of the new indication.

RALES is useful for supporting the concept that aldosterone blockers have efficacy in treating HF. Comparing the RALES and EPHEBUS results may also be useful to identify limitations of treatment, real subgroup differences, and potential mechanisms of action. RALES and EPHEBUS are compared below in a series of tables.

The following table compares general design features and major results of the two studies.

Table 95: Reviewer's General Features and Major Results of EPHEBUS and RALES

	EPHEBUS	RALES
Study population	Stable HF post-MI	Class III-IV HF
Drug mean daily dose	Eplerenone 43 mg	Spironolactone 26 mg
N	6,632	1,663
Whites	90%	87%
Males	71%	73%
Age – median (interquartile)	65 (55-73)	67 (59-73)
US	9%	3%
Weeks – median (interquartile)	70 (52-89)	103 (58-130)
Complete follow-up	99.7%	96%
Baseline ACEI	85%	91%
Baseline loop diuretic	55%	99%
Baseline beta blocker	75%	9%
NYHA class 3	17%	72%
NYHA class 4	2%	27%
Ejection fraction – mean	0.33	0.26
Mortality risk ratio	0.85 (0.75-0.96)	0.70 (0.6-0.82)
Mortality difference p value	0.008	<0.001
Deaths	1032	670
Excess placebo deaths	78	102
Excess placebo sudden deaths	39 (51%)	28 (27%)
Excess placebo HF deaths	23 (30%)	62 (61%)
Deaths within 30 days	34%	8%

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	EPHESUS	RALES
Median potassium change, meq/L	0.25	0.25
Placebo potassium change	0.1	0.0

COMMENT: Besides the drug, the post-MI nature of EPHESUS, and the more severe HF in RALES, there are some other pertinent differences between the two studies. RALES had an eligibility criterion for loop diuretic and ACEI use, so the use of loop diuretics was universal in RALES and the ACEI use was very high. Conversely, RALES is the older study performed at a time when beta blocker use for HF was starting, so beta blocker use in RALES is relatively low. RALES is also a smaller study with longer follow-up. EPHESUS appears to be the better study both regarding conduct (e.g., 99.7% complete follow-up) and US participation. The studies are similar with regard to demographics, with RALES having a slightly older population. Elderly white males predominate in both.

Regarding results, while RALES has the more impressive risk reduction and p value, the EPHESUS results are also strong. It is interesting to note that, while the majority (about 80% for each study) of the excess placebo deaths were attributed to sudden deaths or HF deaths, the excesses are roughly reversed: RALES had more placebo HF deaths and EPHESUS had more placebo sudden deaths. One wonders whether this difference is related to the post-MI nature of EPHESUS, with more arrhythmic deaths averted in the immediate post-MI period. 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). (Note that about two-thirds of the excess placebo deaths occurred during the first 30 days.) However, classifying HF death causes is difficult as documented by one study. (Ziesche, Rector et al. 1995) Differences in causes of death must be interpreted cautiously.

Note that the gross changes in serum potassium from baseline to last value were similar in the two studies, although the placebo-subtracted net change is lower in EPHESUS. More evidence regarding the relationship between potassium and efficacy is given below.

In addition to the similarities and differences between EPHESUS and RALES shown in the previous table, there are other concordances and discordances between EPHESUS and RALES regarding subgroups and concomitant medication responses. The concordances are shown in Table 96 and the discordances in Table 97 below.

Table 96: Reviewer's Concordances Between EPHESUS and RALES

	EPHESUS	RALES
Greatest mortality benefit by region	Latin America, W. Europe	Latin America, W. Europe
Mortality by race	All benefit; nonwhites least*	All benefit; nonwhites most*
Mortality by gender	Both benefit	Both benefit
Mortality by NYHA class	All benefit	All benefit
Mortality in diabetics	Higher; all benefit	Higher; all benefit
Mortality benefit for base SBP ≤ 90	Detriment*	No benefit*
Mortality by β blocker use	Increased benefit	Increased benefit
CV mortality benefit by baseline potassium	Greater risk reduction at lower potassiums for 28 day mortality	Greater risk reduction at lower potassiums throughout study

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* Numbers are small, so differences not interpreted as discordances

Table 97: Reviewer's Discordances Between EPHESUS and RALES

	EPHESUS	RALES
Hospitalizations by gender	Higher females, lower males	Lower in both
Mortality vs. hospitalizations by region	Discordant	Consistent except for small #s
Mortality benefit by age	Decreases with age	Increases with age
Mortality benefit age ≥ 75	Slight detriment	Greatest benefit
Mortality with base CrCl ≤30 mL/min	Higher with eplerenone	Lower with spironolactone
Mortality by hypertension history	No benefit without history	Benefit less with history
Mortality by base SBP level	No consistent change	Decreases with increased SBP
Placebo mortality by base potassium	U-shaped	Higher with lower potassium
Mortality benefit by base potassium	Lost at extremes	Relatively flat

The relationship between CV mortality and baseline potassium levels is intriguing. 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 the table below.

Table 98: Relative Risk of CV Death Compared to Placebo by Baseline Potassium Level in EPHESUS and RALES

Baseline potassium	Eplerenone 28-day	Spironolactone Total
≤3.3	0.45	0.46
3.31-3.5	0.42	0.59
3.51-3.7	0.76	0.77
3.71-3.9	0.70	0.81
3.91-4.1	0.75	0.78
4.11-4.5	0.71	0.68
4.51-5	0.62	0.84
>5	1.05	0.81

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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Comparing EPHESUS and RALES is the classic conundrum of whether the glass is half full or half empty. There are enough dissimilarities that one could conclude that RALES is irrelevant to EPHESUS and the proposed indication. On other hand, there are sufficient similarities that one could conclude that RALES supports the concept that aldosterone blockers are effective in reducing mortality in patients with HF with a wide range of severity and different etiologies. I believe the latter for the following reasons:

- The fundamental mechanism of action, aldosterone blockage, is identical for the two drugs. I have not been impressed that eplerenone behaves dramatically differently with regard to efficacy other than its reduced potency compared to spironolactone.
- The benefits are very similar, e.g., a definite mortality benefit with perhaps some effect on reducing morbidity.
- Many of the differences may be related to the difference that EPHESUS tested a population with milder HF but with an acute insult (MI) while RALES tested the sicker, chronic patient with HF.
- The marked benefit in reducing sudden deaths in EPHESUS and the relationship between potassium levels and 28-day CV mortality in EPHESUS and total CV mortality in RALES suggest a similar mechanism for at least part of the benefits.

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VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Eplerenone in HF patients post-MI appears to be reasonably safe. The one potentially dangerous adverse effect (AE), hyperkalemia, was controlled in EPHESUS 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 EPHESUS. The EPHESUS data do suggest some other possible AEs (thyroid dysfunction, adrenal adenomas, and breast cancer) that may be problematic particularly for the hypertension indication.

B. Description of Patient Exposure

EPHESUS provides about 3,800 patient-exposure years (PEY) to eplerenone with a mean dose of 43.5 mg. This review also incorporates the findings from the open-label extension of EPHESUS. EPHESUS patients with potassium levels <5.0 meq/L and serum creatinines <2.5 mg/dL could continue to receive blinded study medication until the database was unblinded. A total of 1361 eplerenone patients received at least one dose of treatment in the double-blind extension.

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. This review compares the AE rates in the HF studies to those in the hypertension studies. It also compares AE rates of eplerenone to those for spironolactone because spironolactone, as another aldosterone blocker, may have shared toxicities as well as different ones. RALES provides over 1,300 patient-exposure years to spironolactone with a mean daily dose at the end of study of 26 mg.

C. Methods and Specific Findings of Safety Review

The major new source of safety information regarding eplerenone is EPHESUS. Study 011 provides limited additional information regarding higher dosages of eplerenone in HF patients. Study 402 has limited interpretability because of its conduct solely in Japan. The safety results of each of these new studies are presented individually in the detailed study reviews in Section VI.C. This integrated review section concentrates on comparing the results (mainly from EPHESUS) with the results from the hypertension trials and to spironolactone.

1. Hyperkalemia

As noted in Table 95 above, the median change in serum potassium levels was the same in EPHESUS and RALES (0.25 meq/L). However, the placebo-subtracted change was

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lower in EPHESUS (0.15 vs. 0.25). The mean change in serum potassium was 0.14 meq/L for the eplerenone 50 mg daily patients in the placebo-controlled hypertension studies. Hence the average effect of eplerenone upon serum potassium appears to be similar in the hypertension and the post-MI HF populations.

The rates of high values for maximum serum potassium (defined as >5.5 meq/L) were nearly identical for EPHESUS and RALES (15.6% vs. 15.5%). That no high maximum values were reported in the placebo-controlled hypertension studies at the 50 mg daily dosage likely reflects a combination of factors: shorter duration of the hypertension studies, no concomitant use of ACE inhibitors or angiotensin receptor blockers, and few patients with reduced renal function.

Hyperkalemia led to withdrawal in 0.7% of eplerenone patients in EPHESUS and in 1.1% of spironolactone patients in RALES compared to 0.3-0.4% of placebo patients in each study. There were no hyperkalemia deaths in study drug patients in either study.

COMMENT: Hyperkalemia appeared to be tolerable in EPHESUS and comparable to that of spironolactone in RALES. That it was tolerable appears to be related to the moderate average dosage (43 mg), monitoring of serum potassium levels, and the detailed dosage schedule given in Table 15.

2. Sex Hormone-Related Adverse Events

Study 011 again confirmed that eplerenone can cause sex hormone-related AEs. Two females on eplerenone experienced breast pain, two males on eplerenone experienced gynecomastia and an additional male on eplerenone experienced breast tenderness, and one male on spironolactone experienced gynecomastia. The breast tenderness occurred at days 20-40 in a patient receiving eplerenone 50 mg QD patient while the gynecomastia occurred in patients receiving 100 mg or more daily after 12 weeks. The case of gynecomastia on spironolactone was early (day 16) and another eplerenone patient was reported to have gynecomastia at baseline. No placebo patients reported these symptoms.

From Study 011 it is not clear whether eplerenone at doses of 100 mg daily and above produces fewer sex hormone-related AEs than spironolactone at 25 mg daily. Similarly, it was not clear from the two hypertension studies that compared eplerenone and spironolactone whether equipotent dosages of each drug differ regarding such AEs. In Study 010 in essential hypertension there were few such AEs during the eight week study period. In Study 018 in primary aldosteronism eplerenone 100-300 mg produced fewer such AEs than spironolactone 75-225 mg QD in 16 weeks but spironolactone was clearly more efficacious in controlling blood pressure.

Few sex hormone-related AEs were reported in EPHESUS and the rates were comparable in the eplerenone and placebo groups. One hint that eplerenone may cause clinically significant sex hormone related AEs is that five of the eplerenone gynecomastia events were considered serious while only one of the placebo gynecomastia events was

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considered serious. In RALES gynecomastia was reported much more frequently in the spironolactone group (9.1%) compared to the placebo group (1.1%). Gynecomastia was reported more frequently in the RALES placebo group than in the EPHESUS placebo group (1.1% vs. 0.4%).

One contributor to the differences in sex hormone-related AE rates in the two studies is the differences in the durations of the two studies. EPHESUS had a median follow-up in the eplerenone group of 495 days (interquartile range 366-629 days). The median time to development of gynecomastia in EPHESUS in the eplerenone group was 491 days (interquartile range 372-674 days). RALES had a median follow-up in the spironolactone group of 736 days (interquartile range 473-920 days). The median time to development of gynecomastia in RALES in the spironolactone group was 677 days (interquartile range 400-867 days).

3. Neoplasms

EPHESUS showed some small but intriguing differences in neoplasm rates between eplerenone and placebo:

- Prostate cancers were less frequent (1 vs. 9) while breast cancers were more frequent (3 vs. 0) with eplerenone. These differences are consistent with an estrogen-like effect of eplerenone that is also consistent with an increased rate of gynecomastia. The experience in RALES is not similar, with equal numbers of breast cancers (1 each) and prostate cancers (2 each) in the spironolactone and placebo groups. In the hypertension studies one treatment-emergent breast cancer and one prostate cancer were reported in the eplerenone arms, but the exposure in the placebo arms is too low for any valid comparison. The EPHESUS findings are suggestive but unsupported. Because the absolute rates are low, they don't negate any benefits in HF post-MI. However, if breast cancer rates are increased by eplerenone, then that effect would be critical for the hypertension indication.
- Two adrenal adenomas or nodular hypertrophy were reported in eplerenone patients. One was an "incidentaloma" found on CT scan of the thorax. The other was found after a brief episode of lumbar pain and was eventually excised. Adrenal adenomas were not reported in RALES or in the hypertension studies. Adrenal "incidentalomas" are not rare and are typically benign. However, it would be helpful to know whether eplerenone does increase their incidence so that an appropriate diagnostic strategy could be developed.
- One thyroid carcinoma was reported in an eplerenone patients. See the discussion of thyroid disorders next.

4. Thyroid Disorders

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In EPHESUS both hyperthyroidism (0.4% vs. 0.3%) and hypothyroidism (0.5% vs. 0.2%) were slightly more frequent with eplerenone than with placebo. Similarly, in RALES both hyperthyroidism (1.0% vs. 0.5%) and hypothyroidism (1.8% vs. 1.2%) were slightly more frequent with spironolactone than with placebo. In Study 011 TSH and thyroxin levels were measured. While TSH levels did not vary significantly, the difference among all groups in mean thyroxin levels and mean free thyroxin levels were statistically significant at week 16, with thyroxin levels in the eplerenone 200 mg group significantly lower than those in the spironolactone group. In the three hypertension studies in which TSH and thyroxin were measured, thyroxin did not vary significantly but there was an eplerenone dose-related increase in TSH levels. All of these results, combined with the existence of an animal model for thyroid dysfunction (see Sections I.E.3 and II.A), suggest that eplerenone has an effect upon thyroid function. A possible effect upon thyroid function is not an issue for the HF post-MI indication. It is relevant to the hypertension indication. If there is a real effect upon thyroid function, clinicians should at least be aware of it particularly for patients on long-term therapy.

5. Thrombotic Events

In EPHESUS most thrombotic AEs were reported with similar frequencies for eplerenone and placebo as shown in Table 66. The exception is arterial thromboses, which were reported in 0.5% of the eplerenone group vs. 0.2% of the placebo group. There is also a suggestion of increased thrombogenicity early in the study. In the first 30 days there were 16 first hospitalizations for stroke vs. 9 for placebo and 7 first hospitalizations for peripheral vascular disease vs. 1 for placebo.

In RALES MIs were reported less frequently with spironolactone than with placebo while other thrombotic AEs were reported with similar frequencies for spironolactone and placebo as shown in Table 94. For this AE type the effects of eplerenone and spironolactone appear to be divergent. In the hypertension trials combined rates of cerebrovascular and peripheral vascular appeared higher in the eplerenone groups as shown in the following table taken from the review of the original NDA submission for the hypertension indication.

Table 99: Reviewer's Cardiovascular AE Rates in the Hypertension Studies

Group	Cerebrovascular		Coronary Artery Disease				Peripheral Vascular Thrombosis							
	%	/PEY	%	/PEY	%	/PEY	%	/PEY	%	/PEY	%	/PEY		
Active	0.2%	0.7	0.8%	2.7	0.4%	1.2	0.5%	1.5						
Coadmin	0.3%	1.3	0.6%	3.3	0.3%	1.3	0.4%	2.0						
Mono	0.5%	1.6	1.1%	3.9	0.3%	1.0	0.9%	2.9	0.2%	0.8	0.2%	0.6	0.1%	0.2
Open label	0.7%	1.5	0.7%	1.5	0.2%	0.4	0.5%	1.2	0.3%	0.8	0.2%	0.4	0.2%	0.4
Placebo			0.3%	1.3			0.3%	1.3						
SL														

Active = active controls, e.g., amlodipine, enalapril; Coadmin = eplerenone coadministered with another antihypertensive
 SL = Spironolactone; MI = myocardial infarction; /PEY = per 100 patient exposure years

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Because the table above combines many different studies with slightly patient populations, the differences in the rates are difficult to interpret. The one results consistent between the hypertension studies and EPHEBUS is that peripheral arterial thromboses, while uncommon, appear to be increased in both.

Some fibrinolytic system markers were measured in some of the hypertension trials. Eplerenone produced a small increase in plasminogen activator inhibitor-1 (PAI-1) and possibly a small increase in t-PA. In an EPHEBUS substudy no statistically significant different changes in PAI-1 or t-PA between the eplerenone and placebo groups were observed.

All of these data suggest that eplerenone could have an effect upon thrombogenicity. However, the effect if any appears to be small and is not an issue for the HF post-MI indication because EPHEBUS clearly demonstrates an improvement in mortality. For the hypertension indication any real effect could only be estimated by a very large outcome trial. The evidence is not sufficient to justify such a trial.

D. Adequacy of Safety Testing

The cumulative exposure to eplerenone in all studies, nearly 5,000 PEYs, is good. EPHEBUS adds valuable information regarding chronic exposure to eplerenone, although the dosage is only half of the highest dose recommended for hypertension. Also, while the median exposure duration was over a year, one needs even longer exposures to address issues regarding whether eplerenone increases breast cancer incidence or causes gynecomastia.

Monitoring for and recording of non-targeted AEs was adequate in the eplerenone studies. Hyperkalemia was a targeted AE in the HF trials and monitoring for it appears to have been good. Some other AEs should also have been targeted specifically as described below:

- Sex hormone-related AEs (such as gynecomastia, breast pain, menstrual disorders, loss of libido, and impotence) were not targeted with special questions in EPHEBUS. While it is somewhat reassuring that the gynecomastia rates in EPHEBUS were similar between eplerenone and placebo and gynecomastia was reported in placebo patients, it would be even more reassuring if the rates were found similar with a targeted detection program.
- Whether eplerenone has another effect upon sex hormone levels remains unclear. Some sex hormones were measured in some of the hypertension trials and in Study 011. Progesterone, a hormone that spironolactone affected in males in some studies, was not measured. There is some evidence that eplerenone may affect sex hormones but the data are inconclusive. In the studies it does not appear that important details,

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such as consistent collection times and, in women, timing relative to menstrual cycles have been addressed. A definitive study addressing these details is needed.

- The pre-clinical studies suggest that eplerenone could have an effect upon thyroid hormones, the measurements of TSH in some hypertension trials suggest but do not show conclusively an effect upon TSH, Study 011 suggests an effect upon thyroxin but not TSH, and both eplerenone in EPHESUS and spironolactone (which shares the pre-clinical mechanism of UGDPT induction) in RALES show increases rates of both hypothyroidism and hyperthyroidism. An adequately-powered substudy of EPHESUS measuring TSH would have been valuable.

E. Summary of Critical Safety Findings and Limitations of Data

The HF studies, principally EPHESUS, did not identify any definite safety issues other than those identified in the hypertension studies. With the dose used in EPHESUS (≤ 50 mg/day), monitoring of serum potassium, and dosage adjustment for hyperkalemia, the major dose-limiting toxicity from the hypertension studies (hyperkalemia) was manageable in post-MI HF patients. While the small, dose-ranging HF Study 011 again confirmed that gynecomastia is an eplerenone adverse effect (AE), the rates of gynecomastia and other sex-hormone related AEs in EPHESUS with eplerenone were not significantly different than placebo rates. 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.

EPHESUS results do suggest several potential AEs that aren't a concern for the HF post-MI indication. One of them could be a problem for the hypertension indication if confirmed. These potential problems are the following:

- Eplerenone (and spironolactone) had slightly higher rates of both hypothyroidism and hyperthyroidism than placebo. 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 the eplerenone group in EPHESUS vs. none in the placebo group. While one was symptomatic, a real increased rate of adrenal adenomas probably needs only physician awareness of the issue. "Incidentalomas" are not uncommon. A moderately increased rate will be difficult to detect.
- The one potential AE that could be problematic for the hypertension indication is breast cancer. In EPHESUS three eplerenone and no placebo patients developed breast cancer. While this difference could be chance, it must be judged in light of other findings: In EPHESUS nine eplerenone and one placebo patients developed

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prostate cancer. Both of these differences, as well as gynecomastia, are consistent with an estrogen-like effect. While the prostate cancer difference is a possible benefit, the breast cancer difference is a possible detriment particularly for chronic use in hypertension.

VIII. Dosing, Regimen, and Administration Issues

EPHESUS used a single dosing scheme. The dose was based on effects upon RAAS hormones relative to spironolactone and the spironolactone dose used in RALES. While the dose selected was reasonable and the results of EPHESUS are favorable both regarding 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.

The optimal dosage is not clear. One can speculate that higher dosages are not appropriate because the risks of adverse effects, as shown in the hypertension trials, would likely increase substantially. Both hyperkalemia and sex hormone-related AEs would become troublesome or intolerable. Conversely, there is one fact that suggests a lower dose may be equally or more effective: About one fourth of the deaths but two-thirds of the mortality difference occurred within the first thirty days. During most of this time the eplerenone dosage was 25 mg daily.

The dosing interval was one day. There is nothing to suggest that once daily dosing is wrong, but neither is there any obvious measure to confirm that it is optimal.

One special population that could benefit from dosage adjustment is the elderly. Particularly the very elderly (= 75 years old) did not appear to benefit from therapy and suffered a higher rate of AEs, e.g., hyperkalemia. That they may have benefited during the first 30 days also suggests that a lower dosage may be appropriate for them.

There are also substantial questions at both ends of the treatment period. Per the protocol patients were not randomized until 48 hours after a myocardial infarction. The benefit with eplerenone in EPHESUS was seen rapidly. There could be additional benefit if eplerenone were administered during the first 48 hours. If one benefit is a reduction in arrhythmias and sudden death, then one would presume that such a benefit would be helpful during the first 48 hours post-MI. This question should be studied further.

At the other end, the optimal length of therapy is not known. While the survival benefit appears to persist throughout the duration of EPHESUS, one does not know whether this is a benefit of continued therapy or a residual effect of earlier therapy. If there is a beneficial effect upon contractility or ventricular remodeling or some other HF attribute or upon arrhythmia development, then one would estimate that continued therapy is

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important. However, two-thirds of the excess placebo deaths occurred within the first 30 days. A shorter duration of therapy might be preferable for some subgroups, e.g., the elderly ≥ 75 in EPHESUS showed a mortality benefit early that turned into a detriment later. Whether this is a real effect or a spurious subgroup chance finding needs to be determined.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor analyzed gender effects in EPHESUS both regarding efficacy and safety. The sponsor concluded that there were no significant variations in efficacy or safety by gender. I concur that there are no proven variations in efficacy or safety by gender demonstrated in EPHESUS. I did find one efficacy variation by gender that is relevant: Hospitalization rates were slightly higher in females treated with eplerenone than with placebo while they were slightly higher in males treated with eplerenone than with placebo. This observation may not reflect any real difference by gender but it casts doubt on the sponsor's proposed indication \uparrow

\uparrow For the primary indication of reduced all cause mortality and for safety there do not appear to be any significant variations by gender. The sponsor's overall investigation of gender effects is adequate.

B. Evaluation of Age, Race, and Ethnicity Effects on Safety or Efficacy

I evaluated age, race, and ethnicity effects in EPHESUS and summarized the findings in Section VI.C.3. The following is a brief summary of the findings:

The major finding regarding age effects on efficacy was that eplerenone seemed to show reduced efficacy in the elderly, i.e., age = 75. (See Table 31.) In a Cox regression of survival age is a highly significant covariate. 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. (See Table 79.) Whether the eplerenone effects in the elderly are real or spurious is impossible to determine from EPHESUS 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.

Regarding race or ethnicity effects, EPHESUS 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

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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%).

C. Evaluation of Pediatric Program

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D. Comments on Data Available or Needed in Other Populations

One set of risk factors that has emerged in both the eplerenone hypertension and the HF trials is the combination of diabetes and proteinuria as a risk factor for hyperkalemia. The available data are adequate to identify these characteristics as risk factors. More information would be helpful to characterize better the nature of the risks, variations in benefit, and whether any dosing adjustments would be useful for minimizing risks and maximizing benefits.

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X. Conclusions and Recommendations

A. Conclusions

EPHESUS demonstrates that eplerenone reduces the risk of death in HF patients post-MI. The risk reduction in EPHESUS was 15% with a reasonable level of significance ($p = 0.008$). The study appears to have been conducted well and there are no major issues or subgroup variations that challenge its validity. Hyperkalemia was tolerable likely due to the monitoring of serum potassium levels and reduction or suspension of dosing if hyperkalemia was detected. Rates of sex-hormone related adverse effects were comparable to placebo rates for the duration of the study and within the limitation that sex-hormone related adverse effects were not specifically addressed.

RALES provides supporting evidence that aldosterone blockers improve survival in patients with HF. Both studies provide evidence suggestive that the mortality benefits may be related to effects upon potassium levels.

B. Recommendations

From a clinical perspective I recommend approval of eplerenone to improve survival of stable patients with left ventricular systolic dysfunction ($LVEF \leq 40\%$) and clinical evidence of congestive heart failure following acute myocardial infarction. My recommendations regarding the proposed labeling are given below.

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

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

/s/

Thomas Marciniak
10/3/03 08:02:40 AM
MEDICAL OFFICER

NDA 21-437/S-002

Inspra (eplerenone) Tablets

The Safety Update is incorporated into the Medical Review. The deaths are included in the discussion of the primary endpoint and the safety data are incorporated into the Integrated Review of Safety.

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SAFETY UPDATE REPORT

Under 314.50(5)(vi)(b), G.D. Searle, LLC shall under section 505(i) of the Act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. The safety update report(s) shall be submitted as follows: (1) 4 months after the initial submission; (2) following receipt of the initial approvable letter and (3) at other times requested by the FDA.

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