1.6. Laboratory Findings

The clinical program included appropriate monitoring of routine hematology, blood chemistry, and urinalysis tests in all studies. More specialized tests (sex hormones, renin-angiotensin system hormones, other hormones including thyroid and cortisol) were performed in specific studies. The range and frequency of tests appears to be adequate for characterizing the effects of eplerenone upon laboratory test values with the possible exception of effects upon TSH levels. The effects upon TSH levels are discussed below.

Prior to the start of the clinical program the sponsor developed upper and lower limits for laboratory values (except for sex hormones and certain tests performed only in special studies) representing values of potential clinical relevance and cutoff values considered to represent lower and upper extremes. These upper and lower mid-range and extreme values were developed following discussion with external safety consultants and are displayed in the figure below.

Reviewer's comment: The cutoff values in the figure below seem very reasonable and are also used in some of the reviewer's analyses.

Laboratory Test	Lower Extreme (L-)	Lower Mid-Range Limit (L)	Higher Mid-Range Limit (H)	Higher Extreme (H+)
Hematology				
White blood cells (WBC)	2.0×10^9/L	4.0×10^9/L	12.0×10^9/L	20.0×10^9/L
Granulocytes/bands	1.00×10^9/L	2.00×10^9/L	11.00×10^9/L	20.00×10^9/L
Lymphocytes	0.50×10^9/L	1.00×10^9/L	6.00×10^9/L	20.00×10^9/L
Eosinophils	N/A	0.00×10^9/L	0.70×10^9/L	0.99×10^9/L
Red blood cells (RBC)	3.0×10^{12}/L	4.0×10^{12}/L	6.3×10^{12}/L	7.5×10^{12}/L
Hemoglobin	7.0 g/dL or > 3.0 g/dL decrease	10.0 g/dL	16.0 g/dL	18.0 g/dL
Hematocrit	0.21 or > 0.10 decrease	0.30	0.50	0.60
Platelets	50×10^9/L	100×10^9/L	450×10^9/L	600×10^9/L
Clinical chemistry				
Bilirubin (total)	N/A	N/A	26 µmol/L	35 µmol/L
AST (SGOT)	N/A	N/A	75 U/L	200 U/L
ALT (SGPT)	N/A	N/A	75 U/L	200 U/L
Alkaline phosphatase	N/A	N/A	200 U/L	500 U/L
Creatinine	N/A	N/A	177 µmol/L	265 µmol/L
BUN	N/A	N/A	10.7 mmol/L	14.3 mmol/L
Glucose	2.2 mmol/L	2.8 mmol/L	8.9 mmol/L	19.4 mmol/L
Uric Acid	119 µmol/L	149 µmol/L	535 µmol/L	714 µmol/L
Creatine phosphokinase (CPK)	N/A	N/A	230 U/L	300 U/L
Sodium	120 mmol/L	135 mmol/L	150 mmol/L	160 mmol/L
Potassium	2.0 mmol/L	3.5 mmol/L	5.0 mmol/L	5.5 mmol/L
Chloride	80 mmol/L	90 mmol/L	115 mmol/L	130 mmol/L
Bicarbonate	15 mmol/L	20 mmol/L	30 mmol/L	35 mmol/L
Calcium	> 15% below Baseline, or < 1.70 mmol/L	2.00 mmol/L	2.74 mmol/L	3.74 mmol/L
Inorganic phosphorus	0.32 mmol/L	0.97 mmol/L	1.61 mmol/L	2.42 mmol/L
Magnesium	0.35 mmol/L	0.65 mmol/L	1.30 mmol/L	1.50 mmol/L
Cholesterol (total)	N/A	3.10 mmol/L	10.00 mmol/L	11.00 mmol/L
Triglycerides	N/A	0.11 mmol/L	2.83 mmol/L	5.65 mmol/L
Total protein	30 g/L	55 g/L	90 g/L	100 g/L
Albumin	20 g/L	30 g/L	60 g/L	75 g/L
Glutamyl Transferase	N/A	N/A	100 U/L	150 U/L
Coagulation				
Prothrombin time (PT)	N/A	N/A	18.0 sec	36.0 sec
Urinalysis				
Protein	N/A	N/A	Trace	1+ (300 mg/24h)
Glucose	N/A	N/A	Trace	1+ (1 g/24h)
PH	N/A	4.0	8.0	8.5
Specific gravity	N/A	1.003	1.030	1.040
RBC	N/A	0/hpf	5/hpf	10/hpf
WBC	N/A	0/hpf	10/hpf	20/hpf
Ketones	N/A	N/A	1+	3+
Urine bilirubin	N/A	N/A	Negative	2+

Figure 31: Sponsor's Prospective Mid-Range and Extreme Value Limits for Evaluation of Clinical Laboratory Tests

1.6.1. Hematology

The mean changes from baseline in hematology values, shown in the table below, were small and similar among the treatment groups in the combined controlled trials.

Laboratory Test (unit)	Placebo (N=375)		Eplerenone Monotherapy (N=1748)		Eplerenone Coadministration Therapy (N=772)		Active Comparators (N=1422)	
Hemoglobin (g/dL)	14.26	(0.05)	14.40	(0.06)	14.54	(-0.03)	14.42	(0.01)
Hematocrit (%)	0.424	(0.002)	0.427	(0.000)	0.434	(-0.005)	0.425	(-0.002)
RBC ($\times 10^{12}$/L)	4.77	(0.04)	4.80	(0.01)	4.82	(-0.01)	4.81	(0.00)
Platelet count ($\times 10^{9}$/L)	248.6	(-0.4)	241.8	(3.2)	240.2	(5.8)	242.3	(3.3)
WBC ($\times 10^{9}$/L)	6.15	(0.15)	6.33	(0.24)	6.53	(0.20)	6.41	(0.18)
Neutrophil count ($\times 10^{9}$/L)	3.622	(0.123)	3.837	(0.150)	3.914	(0.096)	3.837	(0.150)
Band count ($\times 10^{9}$/L)	0.000	(0.000)	0.000	(0.000)	0.000	(0.000)	0.000	(0.000)
Lymphocyte count ($\times 10^{9}$/L)	1.923	(0.034)	1.890	(0.085)	2.014	(0.088)	1.977	(0.027)
Monocyte count ($\times 10^{9}$/L)	0.364	(-0.004)	0.371	(0.006)	0.385	(0.020)	0.375	(-0.003)
Eosinophil count ($\times 10^{9}$/L)	0.185	(-0.005)	0.175	(0.004)	0.155	(-0.001)	0.159	(0.005)
Basophil count ($\times 10^{9}$/L)	0.050	(-0.001)	0.050	(0.001)	0.056	(0.001)	0.053	(-0.002)

Source: Table T11.1.1.
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 026, and 049; no additional antihypertensive medication data included.
Data are expressed as mean Baseline (mean change to Final Visit).
N/A=not applicable

Figure 32: Sponsor's Mean Baseline and Changes in Hematology Values for Controlled Trials

Low and high mid-range hematology values at the final visit with an incidence ≥2% in any treatment group in the combined controlled trials are presented in the figure below. The incidence of high mid-range hemoglobin values at the final visit was slightly higher among patients who received eplerenone as either monotherapy or as part of coadministration therapy compared to patients who received active comparators. No other remarkable differences among the treatment groups were noted for the incidence of mid-range hematology values. In particular outlier values for platelet counts were rare and were evenly distributed among groups.

Laboratory Test and Mid-Range Criterion	Placebo		Eplerenone Monotherapy		Eplerenone Coadministration Therapy		Active Comparators	
Low Mid-Range								
WBC < 4.0 x 10^9/L	10/339	(2.9)	29/1634	(1.8)	6/730	(0.8)	24/1327	(1.8)
Neutrophil Count < 2.00 x 10^9/L	7/340	(2.1)	26/1633	(1.6)	8/734	(1.1)	21/1325	(1.6)
Lymphocyte Count < 1.00 x 10^9/L	8/348	(2.3)	18/1649	(1.1)	11/737	(1.5)	14/1342	(1.0)
High Mid-Range								
Hemoglobin > 16.0 g/dL	16/331	(4.8)	88/1569	(5.7)	45/704	(6.4)	50/1262	(4.0)
Hematocrit > 0.50	8/349	(2.3)	29/1652	(1.8)	15/732	(2.0)	21/1330	(1.6)

Source: Table T12.1.1.
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 026, and 049, no additional antihypertensive medication data included.
Data are expressed as no. of patients with mid-range value/no. of patients tested (% of patients).

Figure 33: Sponsor's Low and High Mid-Range Hematology Values at the Final Visit With ≥2% Incidence in Any Treatment Group: Combined Controlled Trials

The sponsor's analyses of shifts from baseline to final values includes the following pertinent findings:

- Four of 1662 (0.24 %) eplerenone monotherapy, 3 of 741 (0.4 %) coadministration, and 2 of 1346 (0.15 %) active control vs. 0 placebo patients had final hemoglobin values < 7.0 gm/dL or a 3.0 g/dL decrease.

- One of 1662 (0.06 %) eplerenone monotherapy, 1 of 741 (0.13 %) coadministration, and 2 of 1346 (0.15 %) active control vs. 0 placebo patients had final neutrophil values < 1.0 x 10^9/L.

All of the extreme hemoglobin shifts were due to decreases of 3.0 and not to values < 7.0 gm/dL. As the sponsor's numbers above indicate, extreme shifts were not more common in the eplerenone groups compared to active controls. The reviewer did not find any significant dose-response relationships by ANOVA using a continuous dose factor and base value covariate. The reviewer also did not find any differences by gender. The reviewer's mean changes in selected hematologic values from baseline for the controlled trials are shown in the table below and for placebo-controlled trials in the following table.

Table 32: Reviewer's Mean Changes in Selected Hematologic Values from Baseline for Controlled Trials

Group	N	Hemoglobin	WBC	Neutrophils	Platelets
Active	1420	-0.06	0.24	0.18	5.7
Coadmin	857	-0.12	0.23	0.12	5.2
Mono	1661	-0.05	0.23	0.15	3.0
Placebo	375	0.03	0.12	0.07	0.1

Table 33: Reviewer's Changes in Selected Hematologic Values from Baseline for Placebo-Controlled Trials

Group	N	Hemoglobin	WBC	Neutrophils	Platelets
Active	337	0.02	0.29	0.19	5.2
Coadmin	309	0.15	0.36	0.22	6.6
Mono	960	-0.03	0.18	0.12	3.6
Placebo	375	0.03	0.12	0.07	0.1

Note that the changes for eplerenone monotherapy for hemoglobin appear to be consistently negative, although the changes are not statistically significantly different than placebo. Changes for white cell counts and platelets are positive for all groups. The reviewer's numbers may differ slightly from the sponsor's because the reviewer did not exclude other antihypertensive medications and the algorithms for selecting a final value when the patient terminates prematurely may differ.

The sponsor's summary of the hematology results is the following:

"• No clinically meaningful differences in mean changes from Baseline, mid-range values, or shift table analyses for hematology laboratory parameters were observed for eplerenone-treated patients.

"• Higher than expected increases in hemoglobin values were observed across all treatment groups including placebo."

Reviewer's comment: The reviewer did not observe higher than expected increases in hemoglobin values across all groups. Extreme drops in hemoglobin were rare but may be more frequent in the active treatment groups compared to placebo, particularly in the coadministration group. Changes in platelet counts were minimal in all groups. Possibly related adverse events are discussed below in the Review of Systems.

1.6.2. Serum Chemistry

1.6.2.1. Sponsor's Analyses of Serum Chemistry

The mean baseline and changes for the chemistry values for the combined clinical trials are shown in the figure below.

Laboratory Test (unit)	Placebo (N=375)		Eplerenone Monotherapy (N=1748)		Eplerenone Coadministration Therapy (N=772)		Active Comparators (N=1422)	
Total Bilirubin (µmol/L)	8.3	(0.0)	9.4	(-0.4)	8.8	(-0.2)	8.8	(-0.1)
Alkaline Phosphatase (U/L)	73.4	(2.0)	72.9	(0.4)	74.8	(-1.6)	74.7	(1.4)
AST/SGOT (U/L)	23.3	(0.3)	22.7	(0.7)	22.8	(1.0)	22.6	(0.8)
ALT/SGPT (U/L)	24.1	(0.7)	24.8	(1.6)	25.3	(1.2)	24.9	(0.8)
LDH (U/L)	158.2	(-11.6)	149.4	(-4.3)	N/A	N/A	149.5	(-13.4)
GGT (U/L)	34.1	(2.1)	33.0	(3.6)	33.9	(1.6)	31.7	(1.5)
Creatine Kinase (U/L)	211.6	(-50.5)	135.2	(-7.6)	129.5	(-7.5)	130.9	(-4.5)
Creatinine (µmol/L)	76.3	(0.1)	77.8	(3.0)	74.5	(4.9)	74.6	(2.7)
BUN (mmol/L)	4.98	(0.00)	5.36	(0.54)	5.70	(0.60)	5.60	(0.27)
Sodium (mmol/L)	141.1	(0.0)	141.1	(-0.7)	140.9	(-1.2)	141.2	(-0.2)
Potassium (mmol/L)	4.22	(-0.02)	4.24	(0.18)	4.31	(0.12)	4.25	(0.07)
Chloride (mmol/L)	104.7	(-0.1)	104.8	(-0.5)	104.4	(-1.1)	104.7	(-0.4)
Bicarbonate (mmol/L)	25.1	(-0.3)	25.4	(-1.0)	25.7	(-0.2)	25.5	(-0.4)
Uric Acid (µmol/L)	336.6	(4.5)	339.4	(18.8)	339.8	(35.3)	340.9	(-2.4)
Glucose (mmol/L)	5.78	(-0.05)	5.97	(0.14)	6.29	(0.10)	6.10	(0.11)
Total Protein (g/L)	73.4	(0.5)	72.2	(0.8)	71.9	(0.6)	71.9	(0.3)
Albumin (g/L)	40.2	(0.5)	40.3	(0.3)	40.4	(0.1)	40.1	(0.3)
Calcium (mmol/L)	2.305	(0.029)	2.299	(0.052)	2.279	(0.044)	2.279	(0.046)
Inorganic Phosphorus (mmol/L)	1.096	(0.021)	1.095	(0.023)	1.118	(0.029)	1.102	(0.027)
Magnesium (mmol/L)	0.845	(-0.004)	0.841	(-0.020)	0.834	(-0.010)	0.845	(-0.015)
Cholesterol (mmol/L)	5.190	(0.102)	5.313	(0.17)	5.419	(0.106)	5.389	(0.068)
HDL cholesterol (mmol/L)	N/A	N/A	1.273	(0.009)	1.275	(-0.031)	1.279	(-0.012)
Indirect LDL cholesterol (mmol/L)	3.013	(0.065)	3.202	(0.007)	3.305	(-0.015)	3.257	(0.041)
Triglycerides (mmol/L)	1.732	(0.075)	1.840	(0.200)	1.891	(0.311)	1.834	(0.006)

Source: Table T11.1.1.
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 026, and 049; no additional antihypertensive medication data included.
Data are expressed as mean Baseline (mean change to Final Visit).
N/A=not applicable

Figure 34: Sponsor's Mean Baseline and Changes in Chemistry Values for Controlled Trials

The sponsor's discussion of the figure above is the following: "In general, the mean changes from Baseline in serum chemistry parameters were similar between the placebo, eplerenone monotherapy, eplerenone coadministration therapy, and active comparator treatment groups. Although small and not considered meaningful, differences in mean changes were observed for uric acid, creatinine, BUN, potassium and sodium. The increase in mean change from Baseline for triglycerides observed in eplerenone-treated patients seems to have occurred mostly in patients with dyslipidemia at Baseline and in patients with type 2 diabetes. Patients in the eplerenone monotherapy and coadministration therapy groups had greater mean increases in uric acid values and greater mean decreases in sodium values compared to the placebo or active comparator treatment groups. Greater mean increases in creatinine, BUN, glucose, potassium and triglyceride values were observed among patients who received eplerenone or active comparators compared to patients who received placebo."

The mean baseline and changes for the chemistry values for the placebo-controlled trials are shown in the figure below.

Laboratory Test (unit)	Placebo (N=194)		Eplerenone 25 mg (N=97)		Eplerenone 50 mg (N=245)		Eplerenone 100 mg (N=193)		Eplerenone 200 mg (N=139)		Eplerenone 400 mg (N=104)	
Total Bilirubin (µmol/L)	9.6	(0.3)	8.1	(0.5)	10.3	(-0.1)	10.8	(-0.5)	8.8	(-0.2)	12.2	(-0.3)
Direct Bilirubin (µmol/L)	2.3	(0.0)	N/A	N/A	2.5	(-0.1)	2.5	(-0.1)	N/A	N/A	2.4	(-0.1)
Indirect Bilirubin (µmol/L)	8.8	(0.1)	N/A	N/A	9.6	(0.1)	9.7	(-0.3)	N/A	N/A	9.8	(-0.2)
Alkaline phosphatase (U/L)	72.2	(1.2)	71.5	(1.5)	71.2	(-0.5)	72.1	(0.4)	72.1	(0.3)	73.7	(-0.4)
AST/SGOT (U/L)	23.7	(-0.3)	23.1	(0.0)	22.7	(-0.5)	21.1	(0.1)	23.3	(1.4)	18.9	(1.9)
ALT/SGPT (U/L)	24.9	(0.6)	24.3	(0.5)	23.8	(0.8)	23.0	(1.3)	25.2	(1.2)	21.7	(4.7)
LDH (U/L)	158.2	(-11.6)	N/A	N/A	152.1	(-3.8)	149.1	(-2.3)	N/A	N/A	146.9	(-6.8)
GGT (U/L)	33.5	(1.5)	29.1	(1.5)	36.5	(2.9)	32.9	(3.7)	29.8	(3.2)	34.5	(11.4)
Creatine Kinase (U/L)	237.4	(-93.2)	153.8	(-17.5)	139.1	(-13.4)	135.4	(-8.7)	135.0	(5.4)	126.0	(-22.8)
Creatinine (µmol/L)	78.6	(-0.4)	76.5	(-0.5)	82.9	(1.2)	82.8	(0.5)	73.9	(2.0)	95.0	(2.5)
BUN (mmol/L)	5.15	(-0.08)	5.24	(0.03)	5.09	(0.39)	4.97	(0.39)	5.34	(0.46)	5.17	(0.79)
Sodium (mmol/L)	141.1	(0.1)	140.1	(0.2)	141.1	(-0.6)	141.1	(-0.9)	141.1	(-1.1)	140.9	(-1.8)
Potassium (mmol/L)	4.27	(-0.02)	4.28	(0.08)	4.22	(0.14)	4.23	(0.09)	4.25	(0.19)	4.19	(0.36)
Chloride (mmol/L)	104.9	(-0.2)	104.2	(0.3)	105.1	(-0.2)	105.5	(-0.6)	105.0	(-0.7)	105.2	(-1.1)
Bicarbonate (mmol/L)	25.5	(-0.1)	25.6	(-0.5)	25.7	(-0.9)	24.7	(-1.0)	25.6	(-0.9)	N/A	N/A
Uric Acid (µmol/L)	331.9	(4.8)	354.9	(10.3)	340.2	(15.8)	331.4	(18.0)	341.5	(19.1)	306.7	(24.2)
Glucose (mmol/L)	5.72	(0.01)	5.70	(0.08)	5.74	(0.02)	5.82	(0.18)	5.62	(0.22)	5.85	(0.11)
Total Protein (g/L)	72.7	(0.7)	73.1	(0.2)	72.4	(0.4)	72.4	(0.4)	73.2	(0.7)	70.6	(1.9)
Albumin (g/L)	41.2	(0.4)	40.3	(0.3)	40.9	(0.2)	40.9	(0.1)	40.8	(0.1)	41.1	(0.4)
Calcium (mmol/L)	2.326	(0.023)	2.303	(0.016)	2.345	(0.004)	2.354	(0.009)	2.309	(0.030)	2.349	(0.051)
Inorganic Phosphorus (mmol/L)	1.092	(0.021)	1.101	(0.012)	1.108	(0.019)	1.094	(0.001)	1.086	(0.032)	1.062	(0.009)
Magnesium (mmol/L)	0.845	(-0.002)	0.838	(0.004)	0.845	(-0.011)	0.835	(-0.018)	0.841	(-0.018)	0.847	(-0.011)
Cholesterol (mmol/L)	5.235	(0.098)	5.310	(-0.038)	5.387	(0.086)	5.191	(0.088)	5.217	(0.126)	5.319	(0.244)
Triglycerides (mmol/L)	1.687	(0.082)	1.798	(0.111)	1.976	(0.163)	1.992	(0.085)	1.921	(0.103)	1.682	(0.404)

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

Figure 35: Sponsor's Mean Baseline and Changes in Chemistry Values for Placebo-Controlled, Fixed Dose Monotherapy Trials

The sponsor observed the following regarding the results in the above figure: "Trends were observed for ALT/SGPT, GGT, BUN, potassium, creatinine, and uric acid, with greater increases noted with increasing dose. In addition, greater decreases in sodium and magnesium were observed with increasing dose."

The mean baseline and changes for the chemistry values that were significantly different in the eplerenone/hydrochlorothiazide factorial trial (Study 015) are shown in the figure below.

Laboratory Test (unit)	Eplerenone Monotherapy (N=152)		HCTZ (N=102)		p-value
BUN (mmol/L)	5.21	(0.20)	5.23	(0.57)	0.010
Potassium (mmol/L)	4.23	(0.12)	4.26	(-0.19)	< 0.001
Chloride (mmol/L)	103.7	(-0.3)	103.7	(-2.0)	< 0.001
Bicarbonate (mmol/L)	27.0	(-0.4)	27.0	(0.9)	< 0.001
Uric Acid (µmol/L)	347.8	(13.1)	340.7	(46.2)	< 0.001

Source: Table T11.3.
Includes Study 015.
Data are expressed as mean Baseline (mean change to Final Visit), except for p-values, and include any variables for which a significant ($p \leq 0.05$) difference was observed between eplerenone monotherapy and HCTZ for mean change from Baseline to the Final Visit.

Figure 36: Sponsor's Mean Baseline and Changes in Serum Chemistry Values That Were Significantly Different in the Eplerenone/Hydrochlorothiazide Factorial Trial

Note that the effects of HCTZ on BUN, chloride, bicarbonate are in the same direction but greater than those of eplerenone while, as expected, the effects on potassium are divergent between the two drugs. In addition to the significant differences shown in the figure above, the increases in glucose with HCTZ exceeded those with eplerenone and were close to nominal statistical significance. Increases in triglycerides with HCTZ were slightly higher but not significantly different from increases with eplerenone.

The mean baseline and changes for the chemistry values that were significantly different in the trials involving spironolactone (Studies 010 and 018) are shown in the figure below. Spironolactone had a similar but greater effect upon potassium, creatinine, and BUN than eplerenone, but recall that the dosages of spironolactone given in these trials also had a significantly greater antihypertensive effect than the dosages of eplerenone given. Note that eplerenone appears to have a small but significantly greater effect upon ALT and GGT than spironolactone.

The mean baseline and changes for the chemistry values for eplerenone monotherapy in the long-term trials is shown in the following table. The slight changes appear consistent with those observed in the controlled comparisons: a slight increases in ALT, GGT, creatinine, BUN, potassium, uric acid, glucose, and triglycerides and slight decreases in sodium, chloride, and bicarbonate.

Laboratory Test (unit)	Eplerenone Monotherapy (N=386)		Spironolactone (N=119)		p-value
Total Bilirubin (µmol/L)	12.0	(-0.4)	11.9	(-1.2)	0.011
Alkaline Phosphatase (U/L)	72.3	(0.3)	68.7	(-2.9)	< 0.001
AST/SGOT (U/L)	20.1	(0.6)	22.2	(-1.5)	0.037
ALT/SGPT (U/L)	22.8	(2.3)	25.7	(-1.4)	< 0.001
LDH (U/L)	149.4	(-4.3)	149.5	(-13.4)	0.007
GGT (U/L)	34.1	(6.4)	33.0	(1.8)	0.019
Creatinine (µmol/L)	90.0	(2.0)	82.4	(10.3)	< 0.001
BUN (mmol/L)	5.11	(0.60)	5.42	(1.41)	< 0.001
Sodium (mmol/L)	141.2	(-1.4)	141.2	(-2.1)	0.007
Potassium (mmol/L)	4.13	(0.25)	4.04	(0.57)	< 0.001
Albumin (g/L)	41.0	(0.2)	40.7	(1.0)	0.002
Inorganic Phosphorus (mmol/L)	1.074	(0.008)	1.046	(0.061)	0.006
Magnesium (mmol/L)	0.845	(-0.014)	0.855	(-0.034)	0.008

Source. Table T11.4.
Includes Studies 010 and 018.
Data are expressed as mean Baseline (mean change to Final Visit), except for p-values, and include any variables for which a significant ($p \leq 0.05$) difference was observed between eplerenone monotherapy and spironolactone for mean change from Baseline to the Final Visit.

Figure 37: Sponsor's Mean Baseline and Changes in Serum Chemistry Values That Were Significantly Different in the Trials Involving Spironolactone

Laboratory Test (unit)	Eplerenone Long-Term Monotherapy (N=1130)	
Total Bilirubin (µmol/L)	9.4	(-0.7)
Alkaline Phosphatase (U/L)	72.5	(1.7)
AST/SGOT (U/L)	23.5	(0.5)
ALT/SGPT (U/L)	26.4	(1.2)
GGT (U/L)	32.8	(3.4)
Creatine Kinase (U/L)	125.5	(-6.9)
Creatinine (µmol/L)	74.5	(3.8)
BUN (mmol/L)	5.56	(0.57)
Sodium (mmol/L)	140.5	(-0.2)
Potassium (mmol/L)	4.29	(0.18)
Chloride (mmol/L)	104.4	(-0.4)
Bicarbonate (mmol/L)	26.0	(-0.9)
Uric Acid (µmol/L)	349.0	(15.8)
Glucose (mmol/L)	6.14	(0.14)
Total Protein (g/L)	71.6	(1.1)
Albumin (g/L)	39.8	(0.7)
Calcium (mmol/L)	2.261	(0.081)
Inorganic Phosphorus (mmol/L)	1.093	(0.026)
Magnesium (mmol/L)	0.851	(-0.030)
Cholesterol (mmol/L)	5.397	(0.140)
HDL Cholesterol (mmol/L)	1.164	(0.007)
Indirect LDL Cholesterol (mmol/L)	3.097	(-0.021)
Triglycerides (mmol/L)	1.982	(0.193)

Source. Table T11.12.
Includes Studies 016, 017, 021, 022, and 025, no additional antihypertensive medication data included.
Data are expressed as mean Baseline (mean change to final visit).

Figure 38: Sponsor's Mean Baseline and Changes in Serum Chemistry Values for Patients Receiving Eplerenone Monotherapy in the Long-Term Trials

The final visit chemistry values outside of the low and high mid-range values with at least two percent incidence in any treatment group are shown in the table below.

Laboratory Test and Mid-Range Criterion	Placebo		Eplerenone Monotherapy		Eplerenone Coadministration Therapy		Active Comparators	
Low Mid-Range								
Sodium < 135 mmol/L	1/351	(0.3)	15/1682	(0.9)	25/748	(3.3)	12/1366	(0.9)
Bicarbonate < 20 mmol/L	9/294	(3.1)	45/1368	(3.3)	18/743	(2.4)	21/1313	(1.6)
Inorganic Phosphorus < 0.97 mmol/L	32/340	(9.4)	121/1609	(7.5)	65/715	(9.1)	98/1306	(7.5)
High Mid-Range								
GGT > 100 U/L	7/345	(2.0)	32/1656	(1.9)	10/738	(1.4)	22/1356	(1.6)
Creatine Kinase > 230 U/L	21/312	(6.7)	67/1605	(4.3)	28/728	(3.8)	65/1303	(5.0)
Potassium > 5.0 mmol/L	4/368	(1.1)	74/1702	(4.3)	47/756	(6.2)	43/1403	(3.1)
Bicarbonate > 30 mmol/L	6/294	(2.0)	21/1368	(1.5)	25/743	(3.4)	32/1313	(2.4)
Uric Acid > 535 µmol/L	7/348	(2.0)	35/1674	(2.1)	37/741	(5.0)	20/1361	(1.5)
Glucose > 8.9 mmol/L	9/347	(2.6)	47/1641	(2.9)	32/708	(4.5)	42/1306	(3.2)
Triglycerides > 2.83 mmol/L	22/330	(6.7)	142/1573	(9.0)	67/682	(9.8)	74/1279	(5.8)

Source. Table T:2.1.1.
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023 024, 026, and 049; no additional antihypertensive medication data included.
Data are expressed as no. of patients with mid-range value/no. of patients tested (% of patients).

Figure 39: Sponsor's Low and High Mid-Range Serum Chemistry Values at the Final Visit With ≥2% Incidence in Any Treatment Group: Combined Controlled Trials

Note that these tests are about the same as the ones for which eplerenone seems to have an effect upon mean values. However, the eplerenone monotherapy values at the final visit in the figure above are more extreme than placebo only for sodium, potassium, and triglycerides and the eplerenone coadministration values are more extreme for sodium, potassium, bicarbonate, glucose and triglycerides.

For some tests, the maximum values at any time during the treatment period appear to be more revealing. The final visit and maximum values exceeding the high mid-range reference values for liver function tests, taken from sponsor's Table 1.2.1, are shown in the figure below. Note that for ALT and GGT the eplerenone monotherapy and coadministration incidences exceed the placebo rates for the maximum values but not for the final visit values. A similar pattern exists for the renal function tests and electrolytes shown in the second figure below. The only other tests that appeared to have clinically significant differentials for this outlier analysis were glucose and triglycerides. The rates for glucose and triglycerides are shown in the third figure below. Included in that figure are the rates for urine glucose as well.

Lab Test - High Midrange Criteria	Placebo	Eplerenone Monotherapy	Co-Admin Therapy	Active Comparators
Total Bilirubin - Above 26 umol/L				
Final Visit	3/351 (0.9)	4/1682 (0.2)	1/744 (0.1)	4/1361 (0.3)
Maximum Value	4/351 (1.1)	20/1682 (1.2)	4/744 (0.5)	8/1361 (0.6)
Alkaline Phosphatase - Above 200 U/L				
Final Visit	1/351 (0.3)	2/1683 (0.1)	0/748 (0.0)	3/1362 (0.2)
Maximum Value	1/351 (0.3)	5/1683 (0.3)	2/748 (0.3)	5/1362 (0.4)
AST(SGOT) - Above 75 U/L				
Final Visit	1/351 (0.3)	6/1681 (0.4)	4/746 (0.5)	6/1363 (0.4)
Maximum Value	3/351 (0.9)	12/1681 (0.7)	5/746 (0.7)	12/1363 (0.9)
ALT(SGPT) - Above 75 U/L				
Final Visit	6/349 (1.7)	20/1676 (1.2)	13/745 (1.7)	10/1361 (0.7)
Maximum Value	7/349 (2.0)	49/1676 (2.9)	23/745 (3.1)	33/1361 (2.4)
GGT - Above 100 U/L				
Final Visit	7/345 (2.0)	32/1656 (1.9)	10/738 (1.4)	22/1356 (1.6)
Maximum Value	9/345 (2.6)	58/1656 (3.5)	27/738 (3.7)	39/1356 (2.9)

Figure 40: Sponsor's Final Visit and Maximum Values Exceeding the High Mid-range Reference Values for Combined Clinical Trials (Liver Function Tests)

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Lab Test - High Midrange Criteria	Placebo	Eplerenone Monotherapy	Co-Admin Therapy	Active Comparators
Creatinine - Above 177 umol/L				
Final Visit	0/352 (0.0)	3/1685 (0.2)	1/749 (0.1)	1/1366 (<0.1)
Maximum Value	0/352 (0.0)	7/1685 (0.4)	6/749 (0.8)	1/1366 (<0.1)
BUN - Above 10.7 mmol/L				
Final Visit	0/351 (0.0)	21/1681 (1.2)	13/748 (1.7)	16/1362 (1.2)
Maximum Value	0/351 (0.0)	41/1681 (2.4)	47/748 (6.3)	37/1362 (2.7)
Sodium - Above 150 mmol/L				
Final Visit	0/351 (0.0)	0/1682 (0.0)	0/748 (0.0)	2/1366 (0.1)
Maximum Value	1/351 (0.3)	1/1682 (<0.1)	1/748 (0.1)	5/1366 (0.4)
Sodium - Below 135 mmol/L (Low Midrange Criteria)				
Final Visit	1/351 (0.3)	15/1682 (0.9)	25/748 (3.3)	12/1366 (0.9)
Minimum Value	2/351 (0.6)	47/1682 (2.8)	55/748 (7.4)	32/1366 (2.3)
Potassium - Above 5.0 mmol/L				
Final Visit	4/368 (1.1)	74/1702 (4.3)	47/756 (6.2)	43/1403 (3.1)
Maximum Value	20/368 (5.4)	316/1702 (18.6)	135/756 (17.9)	230/1403 (16.4)
Chloride - Above 115 mmol/L				
Final Visit	0/351 (0.0)	1/1684 (<0.1)	0/748 (0.0)	1/1366 (<0.1)
Maximum Value	0/351 (0.0)	2/1684 (0.1)	1/748 (0.1)	1/1366 (<0.1)
Bicarbonate - Above 30 mmol/L				
Final Visit	6/294 (2.0)	21/1368 (1.5)	25/743 (3.4)	32/1313 (2.4)
Maximum Value	10/294 (3.4)	77/1368 (5.6)	48/743 (6.5)	93/1313 (7.1)
Uric Acid - Above 535 umol/L				
Final Visit	7/348 (2.0)	35/1674 (2.1)	37/741 (5.0)	20/1361 (1.5)
Maximum Value	12/348 (3.4)	77/1674 (4.6)	68/741 (9.2)	38/1361 (2.8)
Calcium - Above 2.74 mmol/L				
Final Visit	0/351 (0.0)	2/1685 (0.1)	1/748 (0.1)	0/1365 (0.0)
Maximum Value	0/351 (0.0)	5/1685 (0.3)	2/748 (0.3)	0/1365 (0.0)
Inorganic Phosphorus - Above 1.61 mmol/L				
Final Visit	1/340 (0.3)	7/1609 (0.4)	4/715 (0.6)	8/1306 (0.6)
Maximum Value	2/340 (0.6)	32/1609 (2.0)	16/715 (2.2)	34/1306 (2.6)

Figure 41: Sponsor's Final Visit and Maximum Values Exceeding the High Midrange Criteria for Combined Clinical Trials (Renal Function Tests and Electrolytes)

Lab Test - High Midrange Criteria	Placebo	Eplerenone Monotherapy	Co-Admin Therapy	Active Comparators
Glucose - Above 8.9 mmol/L				
Final Visit	9/347 (2.6)	47/1641 (2.9)	32/708 (4.5)	42/1306 (3.2)
Maximum Value	12/347 (3.5)	92/1641 (5.6)	53/708 (7.5)	74/1306 (5.7)
Urine Glucose - Above TRACE				
Final Visit	1/343 (0.3)	19/1582 (1.2)	9/716 (1.3)	25/1255 (2.0)
Maximum Value	1/343 (0.3)	36/1582 (2.3)	16/716 (2.2)	35/1255 (2.8)
Triglycerides - Above 2.83 mmol/L				
Final Visit	22/330 (6.7)	142/1577 (9.0)	68/685 (9.9)	75/1282 (5.9)
Maximum Value	39/330(11.8)	276/1577(17.5)	127/685(18.5)	162/1282(12.6)

Figure 42: Sponsor's Final Visit and Maximum Values Exceeding the High Midrange Criteria for Combined Clinical Trials (Glucose and Triglycerides)

The NDA also includes individual patient analyses of changes in laboratory values. The sponsor's summary of the changes in all liver function tests for patients having an ALT elevation greater than 3 times normal is shown in the figure below. Note that one patient on eplerenone monotherapy also developed a bilirubin value 2.3 times normal and one patient each on coadministration and long-term developed borderline high bilirubin values (21). All patients were male, the patient on the long-term study was treated with 100 mg QD and had an elevated ALT at baseline and the other two patients were treated with 200 mg QD.

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Study	Patient	Day	AST/ SGOT (U/L)	ALT/ SGPT (U/L)	Total Bilirubin (µmol/L)	Alkaline Phosphatase (U/L)
Placebo Cases						
049	2273	31	97	263 (6X)	3	149 (1.3X)
Eplerenone Monotherapy Cases						
016	026	85 87 99	232 (6X) 83 20	472 (10X) 276 (6X) 45	50 (2.3X) 15 15	271 (2.4X) 259 (2.3X) 164 (1.4X)
016	85	55	66	128 (3X)	8	109
016	400	198	178 (4X)	386 (8X)	9	136
018	131	43 47	197 (5X) 68	340 (7X) 210 (4X)	3 3	64 54
020	1130	113 131	124 (3X) 105 (3X)	146 (4X) 124 (3X)	7 5	91 95
021	2370	72	112 (3X)	129 (4X)	10	65
021	2266	30	99	140 (3X)	5	95
022	225	176	148 (4X)	128 (4X)	9	82
Eplerenone Coadministration Cases						
015	674	29	100	209 (4X)	21	280 (2.5X)
021	2609	57	42	102 (3X)	7	81
023	2207	28	54	136 (4X)	3	121
Eplerenone Long-Term Study Cases						
025	37	50	50	130 (3X)	21	65
025	86	18	65	130 (3X)	10	88
025	455	16	54	143 (3X)	10	99
Active Comparator Cases						
016	362	14	47	177 (4X)	12	56
019	161	118	84	122 (3X)	9	108
020	1324	113	64	155 (4X)	9	143 (1.3X)
021	2373	46	47	133 (3X)	17	162 (1.4X)
021	3047	71	166 (4X)	217 (6X)	12	355 (3.2X)
023	2113	55	523 (15X)	603 (17X)	15	155 (1.4X)

Source: Appendix 9.1 through 9.14
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 025, 026, and 049.
Data are expressed as actual values (X-fold elevation from upper limit of normal).
(Table 12.n)

Figure 43: Sponsor's Liver Function Tests in Patients Who Developed an ALT/SGPT Value at Least 3X the Upper Limit of Normal

The NDA also includes an extensive set of tables showing shifts in laboratory values from baseline cross-tabulated by the prespecified mid-range and extreme values described previously. These tables did not suggest any other potential problems that have not been suggested by the previous analyses.

The sponsor's summary of the laboratory value changes is the following:

"• Mean changes from Baseline in eplerenone-treated patients were observed for chemistry parameters, notably sodium, potassium, ALT/SGPT, GGT, creatinine, BUN, triglycerides, and uric acid for which dose-related changes were also observed. These changes were small and not clinically meaningful.

"• Changes in mid-range chemistry parameters in eplerenone-treated patients were observed, notably for ALT/SGPT, uric acid, and sodium, without an apparent dose-related change. The increase in mid-range triglycerides observed in eplerenone-treated patients seems to have occurred mostly in patients with dyslipidemia at Baseline and in patients with type 2 diabetes.

"• Changes in mid-range potassium were observed and are discussed in detail in Section 12.3.1."

The NDA provided additional analyses of two lab tests as topics of special interest: potassium and uric acid. The most pertinent statements from the analyses of hyperkalemia are the following:

"In Study 021, the incidence of elevated potassium associated with eplerenone monotherapy was 31.2%. Among patients with diabetic nephropathy manifested by microalbuminuria, an increased sensitivity to the effects of eplerenone on serum potassium was noted, and the threshold for increased susceptibility to elevated potassium appeared to be a creatinine clearance of 100 mL/min. Diabetes itself, in the absence of microalbuminuria or decreased creatinine clearance, did not predispose to elevated potassium (Table 12.yy).

"In summary, elevated potassium may occur with eplerenone administration but the incidence is low in hypertensive patients with normal renal function. Diabetics with nephropathy and patients with decreased creatinine clearance are at increased risk for the development of elevated potassium, particularly at the dose of 200 mg."

The most pertinent statements from the analyses of hyperuricemia are the following:

• The changes in uric acid levels were small and not associated with clinical symptoms (i.e., gout).

• There is no dose response for the incidence of hyperuricemia in the eplerenone monotherapy treatment group.

• The incidence of composite hyperuricemia observed in the eplerenone coadministration group was higher compared to the eplerenone monotherapy, placebo or active comparator treatment groups. The incidence of laboratory-determined hyperuricemia was higher in the eplerenone coadministration group when compared to eplerenone monotherapy.

• The incidence of composite hyperuricemic events in the eplerenone monotherapy group was similar to that observed in the placebo, HCTZ, spironolactone, losartan, and amlodipine groups.

• There was an increased incidence of laboratory-based hyperuricemia criteria in the eplerenone monotherapy group compared to the enalapril group. A significant increase in the composite hyperuricemia criteria and elevated uric acid values was observed in the eplerenone/enalapril coadministration group compared to enalapril monotherapy. These elevations appear to be derived primarily from Study 021, which evaluated diabetic hypertensive patients.

1.6.2.2. Reviewer's Analyses of Serum Chemistry

Liver Function

The reviewer had noted a possible slight, dose-related effect of eplerenone upon liver enzymes in Study 010 (but not in Study 049 alone). The reviewer explored possible differences in liver function tests in the combined controlled trials data sets by ANOVAs with difference from baseline at final visit or maximum difference from baseline as factors and dose or treatment group as covariates. The reviewer confirmed the observation of the sponsor that eplerenone appears to produce slight, statistically-significant, dose-related increases in ALT and GGT and has no detectable effect upon other measures of liver function. The reviewer also examined the changes by gender and found the differences by gender listed in the table below.

Table 34: Reviewer's Mean Changes in Liver Function Tests from Baseline to Final for Placebo-Controlled, Fixed-Dose Trials

Dose	Bilirubin		Alk phos		AST		ALT		GGT	
	F	M	F	M	F	M	F	M	F	M
0	-0.2	0.7	3.3	-0.2	-0.3	0.0	-0.9	1.5	1.4	2.5
25	0.0	0.6	2.2	0.7	0.3	-1.0	-0.1	0.2	2.1	1.4
50	-0.1	-0.1	-0.3	-0.8	0.0	-0.5	0.4	1.0	0.5	4.9
100	-0.6	-0.5	2.5	-0.8	0.5	-0.2	0.8	1.1	3.3	4.1
200	0.2	-0.4	1.6	-1.1	1.9	0.0	1.8	0.4	1.8	3.1
400	-0.1	-0.5	.3	-1.0	1.6	1.9	2.2	6	5	14.4
P*	0.16	0.61	0.34	0.76	0.34	0.23	0.02	0.002	0.11	0.0001

*P by ANOVA with continuous factor dose and covariate base value

Note the slight increases in ALT and GGT, with the increases in males greater than in females.

Spironolactone did not show a similar pattern in effects upon liver function tests. Spironolactone produced slight decreases in bilirubin and alkaline phosphatase with no

statistically significant effects upon other liver enzymes. There did not appear to be any differences in the changes by gender.

In all the combined controlled trials, eplerenone appears to have a similar effects upon maximum change in liver function tests from baseline. The maximum changes in liver function tests by treatment group are shown in the table below:

Table 35: Reviewer's Mean Changes in Liver Function Tests from Baseline to Maximum Value for Combined Controlled Trials

Group	Bilirubin		Alk phos		AST		ALT		GGT	
	F	M	F	M	F	M	F	M	F	M
Active	1.5	2.3	8.5	7.9	5.0	4.8	6.2	6.5	7.6	8.5
Coadmin	1.5	2.1	5.2	7.7	4.1	6.8	5.4	9.2	7.0	14.3
Mono	1.2	2.0	7.1	7.4	4.4	5.5	5.1	10.0	5.8	13.6
Placebo	1.0	2.0	6.0	6.1	3.1	4.2	2.7	6.5	5.7	6.2
P*	0.002	0.3	<0.0001	0.5	0.38	0.02	0.13	0.01	0.32	0.005

*P by ANOVA with continuous factor dose and covariate base value

The changes in ALT and GGT in males in both the monotherapy and coadministration groups in the table above are consistent with the changes from baseline to final. The reviewer did not explore further the apparent differences in bilirubin and alkaline phosphatase in females in the active control group.

Moderate elevations of ALT (>120 U/L) were slightly but not statistically significantly more frequent in the eplerenone monotherapy and coadministration groups (0.7 and 0.6 percent compared to 0.4 percent for active control and 0.2 percent for placebo.) The changes in ALT vary by the baseline ALT level. About 10.6 percent of the patients, fairly evenly distributed among groups, had baseline ALT values greater than 40. Patients with baseline ALT less than or equal to 40 developed extreme increases, i.e., greater than 120, infrequently—0 percent for the placebo groups and 0.3-0.4 percent in the active treatment groups. Patients with baseline ALT greater than 40 developed values greater than 120 much more frequently—placebo 2.4 percent, active control 0.7 percent, eplerenone monotherapy 4.0 percent, and coadministration 2.4 percent.

Elevations in bilirubin (>20 umol/L) were more frequent in the active treatment groups, all about 5 percent, than in placebo (2.7 percent). Elevation of ALT greater than 120 U/L and bilirubin greater than 20 umol/L occurred only in three patients treated with eplerenone.

Reviewer's comment: The summary of these analyses is that eplerenone appears to produce a slight, dose-related increase in ALT and GGT. The increases appear to be greater in males. Being dose-related, the effects were greatest at the highest dose (400 mg/day) used in the initial trial but abandoned because of frequency of hyperkalemia. Significant elevations of liver function tests appear to be rare and not different than active

controls. The possible hepatic adverse events are discussed below in the Review of Systems section.

Renal Function

Eplerenone produced small increases in mean serum creatinine, BUN, potassium, and uric acid values from baseline to final visit and small decreases in mean serum sodium values. The increases were slightly greater for males than for females. At the dosages used these changes were less than the corresponding effects of spironolactone or hydrochlorothiazide (with hydrochlorothiazide producing decreases in serum potassium levels.) The mean changes from baseline to final visit for these tests by treatment group are shown in the table below. As the NDA notes, these changes are statistically significant and dose related but small and, with the exception of potassium and possibly uric acid, probably not clinically significant.

Table 36: Reviewer's Mean Changes in Renal Related Tests from Baseline to Final

Group	Creatinine µmol/L	BUN mmol/L	Sodium mmol/L	Potassium mmol/L	Calcium mmol/L	Uric acid µmol/L
ACEI	3.68	0.33	0.17	0.06	0.07	-0.21
ARB	2.44	0.13	-0.17	0.03	0.04	0.80
BB	-0.51	0.07	-0.22	0.03	0.02	-8.33
CCB	1.79	0.06	0.03	-0.02	0.04	-5.75
Coadmin	4.64	0.48	-0.92	0.06	0.04	33.29
HCTZ	2.64	0.56	-0.81	-0.16	0.02	41.19
Monotherapy	2.82	0.46	-0.53	0.12	0.05	15.34
Open label	2.82	0.44	0.21	0.15	0.08	9.49
Placebo	0.14	0.03	-0.21	-0.04	0.03	5.36
SL	10.21	1.38	-2.04	0.53	0.06	23.71

ACEI = ACE inhibitor (mainly enalapril); ARB = angiotensin receptor blocker (mainly losartan); BB = beta blocker; CCB = calcium channel blocker (mainly amlodipine); HCTZ = hydrochlorothiazide; SL = spironolactone

Hyperkalemia, defined for the following discussion as a maximum potassium value of greater than 5.5, appears to be clinically significant in some circumstances. For all patients treated with eplerenone 400 mg the rate was about 7.8 percent while for lower dosages it was 1 percent or less. The sponsor has stated that hyperkalemia was the reason for abandoning the 400 mg dosage.. For patients with mild renal insufficiency, defined as a baseline creatinine greater than 106 umol/L or 1.2 mg/dL, the rate is 37 percent with combined therapy, 27 percent with an ACE inhibitor alone, and 8 percent with eplerenone alone. However, in Study 021 in diabetics with microalbuminuria, the rates were high for both monotherapy and combination therapy (33 and 39 percent) and somewhat lower for an ACE inhibitor alone (17 percent). The rate was high (29 percent) in Study 021 for eplerenone monotherapy even when the baseline creatinine was normal (<1.0 mg/dL).

Other Tests :

The other tests that showed minor differences from baseline to final in the sponsor's analyses were glucose and triglycerides. The reviewer's analyses did not find any other chemistry tests upon which eplerenone treatment seemed to have an effect. The mean changes from baseline to final in glucose and triglycerides are shown in the table below. The effects of eplerenone upon glucose appear to be lower than that of hydrochlorothiazide and spironolactone; the effects of eplerenone upon triglycerides are similar to those of hydrochlorothiazide. The increases with eplerenone were slightly greater in males than females.

Table 37: Reviewer's Mean Changes in Glucose and Triglycerides from Baseline to Final

Group	Glucose mmol/L	Triglycerides mmol/L
Active	0.12	0.05
Coadmin	0.09	0.25
HCTZ	0.42	0.13
Monotherapy	0.15	0.18
Open label	0.24	0.15
Placebo	-0.02	0.05
SL	0.30	0.06

HCTZ = hydrochlorothiazide; SL = spironolactone

1.6.3. Urinalysis

The NDA presented urinalysis values similarly to the laboratory test values, with extensive tabulations of mean changes from baseline, high mid-range values and shifts from baseline. The one noteworthy finding, a greater incidence of urine glucose readings above trace for eplerenone and active control groups compared to placebo, is shown in a previous figure. No other clinically significant differences were observed.

1.6.4. Hormones

A variety of hormone levels were assessed in some of the trials. Changes in renin-angiotensin system hormones, i.e., aldosterone and renin, are considered in the Integrated Summary of Efficacy. The sponsor's first table in Section 9.4. Hormones of the ISS summarizing the other hormone changes, for the placebo-controlled, fixed-dose monotherapy trials, is shown below:

Laboratory Test (unit)	Placebo (N=194)		Eplerenone 25 mg (N=97)		Eplerenone 50 mg (N=245)		Eplerenone 100 mg (N=193)		Eplerenone 200 mg (N=139)		Eplerenone 400 mg (N=104)	
Estradiol (pg/mL)	35.6	(6.9)	N/A	N/A	39.7	(1.5)	36.8	(7.9)	N/A	N/A	37.0	(0.9)
FSH (IU/L)	21.9	(0.4)	N/A	N/A	14.7	(0.0)	17.8	(0.0)	N/A	N/A	23.0	(1.3)
Luteinizing hormone (IU/L)	12.0	(-0.3)	N/A	N/A	8.7	(0.3)	9.6	(1.0)	N/A	N/A	12.0	(1.4)
Thyroxine (nmol/L)	95.4	(-0.3)	99.3	(-1.6)	94.3	(-1.6)	94.0	(-0.2)	99.1	(-1.7)	90.4	(1.1)
TSH (mU/L)	1.79	(0.16)	1.93	(-0.18)	2.26	(-0.06)	1.79	(0.03)	1.64	(0.27)	1.93	(0.31)
T3RU	0.359	(0.004)	0.354	(-0.001)	0.353	(0.007)	0.359	(0.001)	0.355	(0.001)	N/A	N/A
Total testosterone (ng/dL)	277.9	(1.7)	N/A	N/A	324.0	(3.5)	308.2	(1.6)	N/A	N/A	327.7	12.1
Free testosterone (pg/mL)	71.33	(2.98)	N/A	N/A	78.23	(3.78)	80.04	(0.58)	N/A	N/A	84.29	(4.07)
Dihydrotestosterone (ng/dL)	25.7	(-0.8)	N/A	N/A	28.8	(-1.6)	27.0	(1.6)	N/A	N/A	28.3	(0.5)

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

(Table 9.bbb)

Figure 44: Sponsor's Mean Baseline and Mean Changes From Baseline to the Final Visit in Hormone Values: Placebo-Controlled, Fixed-Dose Monotherapy Trials

The figure above is somewhat misleading. The Ns in the column headings give the total number of patients in the trials, not the numbers of patients with hormone assessments. While Study 015 is a placebo-controlled, fixed-dose monotherapy trial and is listed in the footnote of table below, it does not contribute any hormone data to the figure. Study 049 contributes only to the thyroid hormone statistics. The sex hormone changes are from Study 010 alone. The NDA does caution about this difference between Ns and hormone assessments in the first paragraph of Section 9.4.

Changes in cortisol were assessed in some trials. The sponsor's analysis of changes in cortisol levels from Study 020 is shown in the figure below.

	Placebo			Eplerenone Monotherapy		
		Baseline	Mean		Baseline	Mean
Visit	n	Mean	Change|stderr	n	Mean	Change|stderr
Serum Cortisol (nmol/L)						
Week 16	129	334.90	-14.50|13.232	145	331.93	-15.66| 9.660
Final	129	334.90	-14.50|13.232	145	331.93	-15.28| 9.672

(From Table T11.2.1)

Figure 45: Sponsor's Change in Serum Cortisol from Baseline in Placebo-Controlled Monotherapy Trials

The sponsor also compared differences in some hormone levels between eplerenone and active controls. A significant difference for mean change from baseline to the final visit for cortisol was observed between the eplerenone and spironolactone treatment groups (-3.16 nmol/L and 51.62 nmol/L, respectively). Otherwise hormone levels were comparable.

The sponsor's summary of these hormone changes is the following: "There were no clinically significant changes in thyroid and sex hormone or cortisol values for eplerenone-treated patients." However, the sponsor's ISS in the NDA does not include any analyses of hormones, in particular sex hormones, by gender. A summary of the reviewer's analyses by gender are given below.

Study 010 included the most extensive assessment of sex hormones, including free and total testosterone and dihydrotestosterone, estradiol, FSH, and LH. Study 018 included a "sex profile" consisting of estradiol, total testosterone, and LH. However, Study 018 was not placebo-controlled and included only patients with hyperaldosteronism, so it is not useful for estimating effects upon sex hormones in the general population. The reviewer examined changes in sex hormone levels by gender for Study 010. The results are presented in Appendix B.1 and summarized below.

Table 38: Reviewer's Mean Changes in LH Levels from Baseline to Final for Study 010

Group	Male		Female	
	Change	P	Change	P
0	0.2	0.08	-1.0	0.08
50	0.1		0.6	
100	0.3		2.3	
400	0.6		2.7	
SL	1.1	0.009	-0.1	0.66

SL = spironolactone; P by ANOVA

Table 39: Reviewer's Mean Changes in FSH Levels from Baseline to Final for Study 010

Group	Male		Female	
	Change	P	Change	P
0	0.2	0.006	0.6	0.02
50	0.001		-0.4	
100	-0.2		0.2	
400	-0.4		4.6	
SL	-0.3	0.045	-3.1	0.43

SL = spironolactone; P by ANOVA

Table 40: Reviewer's Mean Changes in Dihydrotestosterone Levels from Baseline to Final for Study 010

Group	Male		Female	
	Change	P	Change	P
0	-2.0	0.03	0.4	0.14
50	-2.2		0.1	
100	1.6		1.5	
400	1.8		-4.1	
SL	-2.9	0.5	-0.8	0.3

SL = spironolactone; P by ANOVA

The sex hormone results are suggestive that eplerenone has a small effect upon pituitary sex hormones. In males the effects are a small decrease in FSH, a small increase in dihydrotestosterone, and possibly a small increase in LH. The effects in females are less clear because of the smaller numbers, particularly for spironolactone. The clinical significance of any of these small changes depends upon whether any important side effects, such as impotence, gynecomastia, breast pain, or menstrual disorders, result.

The reviewer found the following changes in TSH levels for males in Studies 010 and 049:

Table 41: Reviewer's Mean Changes in TSH Levels from Baseline to Final in Study 010

Group	Male		Female	
	Change	P	Change	P
0	-0.02	0.02	0.3	0.83
50	0.09		-0.6	
100	0.03		-0.2	
400	0.36		0.2	
SL	-0.16	0.57	0.41	0.23

SL = spironolactone; P by ANOVA

Table 42: Reviewer's Mean Changes in TSH Levels from Baseline to Final for Study 049

Group	Male		Female	
	Change	P	Change	P
0	0.07	0.03	0.36	0.46
25	0.004		-0.48	
50	0.07		-0.14	
100	0.13		0.06	
200	0.27		0.26	

P by ANOVA

Thyroxin and T3 resin update levels did not differ significantly between the eplerenone and placebo groups. The changes in TSH levels for males between the two studies is remarkably consistent. TSH levels were also evaluated in Study 017. In Study 017 the changes in TSH levels for males for any use of eplerenone compared to no use of eplerenone were not significant, although the mean change for males was again positive. If the data from all three studies are combined, assigning an eplerenone dose of 0 to both placebo and active control groups except spironolactone, and changes in TSH levels are evaluated by ANOVA, dose is a highly significant factor overall (p=0.005) and for males (p = 0.0008) but not for females (p = 0.57). However, gender is not a significant factor in a ANOVA including dose, base value, and gender as factors.

However, note that the greatest increases from baseline in the tables above were recorded for placebo-treated females. The mean changes from baseline for eplerenone vs. placebo in Studies 010 and 049 are listed in the table below:

Table 43: Reviewer's Mean Changes from Baseline in TSH from Studies 010 and 049

	Female		Male		Total	
	Mean	N	Mean	N	Mean	N
Placebo	0.34	65	-0.02	115	0.11	180
Eplerenone	-0.07	227	0.15	368	0.06	595
Total	0.02	292	0.11	483	0.07	775

The mean value at baseline for TSH was 1.87. The maximum mean increase from baseline, in the eplerenone 400 mg group for males, was 0.36, or a relative increase of about 19 percent.

The reviewer also examined outliers and shifts of TSH values from baseline. Thirty-nine patients had TSH levels greater than 5.0 at baseline and 15 patients had levels greater than 10.0 at baseline; 40 patients had TSH levels greater than 5.0 at the final visit and 15 patients had levels greater than 10.0 at the final visit. The higher values were slightly more common in the eplerenone groups at baseline and slightly less at the final visit. Shifts from <= 5.0 to > 5.0 were most frequent among placebo-treated females (5.2 percent), less common among eplerenone-treated females (1.8 percent), infrequent among eplerenone-treated males (0.64 percent), and not found with placebo-treated males. Rates of borderline high TSH values at baseline and final visit are summarized in the table below. There do not appear to be differences among the groups.

Table 44: Reviewer's Rates of High TSH Values at Baseline and Final Visits

Group	Gender	N	Baseline		Final	
			>5	>10	>5	>10
Active	Both	71	0.0%	0.0%	2.8%	0.0%
Active	F	27	0.0%	0.0%	7.4%	0.0%
Active	M	44	0.0%	0.0%	0.0%	0.0%

Group	Gender	N	Baseline		Final	
			>5	>10	>5	>10
Coadmin	Both	67	1.5%	0.0%	3.0%	0.0%
Coadmin	F	22	4.5%	0.0%	4.5%	0.0%
Coadmin	M	45	0.0%	0.0%	2.2%	0.0%
Monotherapy	Both	686	3.9%	1.3%	3.5%	1.2%
Monotherapy	F	264	4.9%	2.7%	5.3%	1.5%
Monotherapy	M	422	3.3%	0.5%	2.4%	0.9%
Placebo	Both	143	2.8%	0.0%	4.2%	0.7%
Placebo	F	58	5.2%	0.0%	10.3%	1.7%
Placebo	M	85	1.2%	0.0%	0.0%	0.0%
Spironolactone	Both	48	6.3%	4.2%	4.2%	4.2%
Spironolactone	F	12	0.0%	0.0%	0.0%	0.0%
Spironolactone	M	36	8.3%	5.6%	5.6%	5.6%

Overall the reviewer interpreted these findings as suggestive that eplerenone produces slight increases in TSH levels of uncertain clinical significance. Whether this effect varies by gender or whether the apparent differences represent random subgroup variations is not clear, although the consistency between Study 010 and Study 049 is suggestive of a gender effect. Please see the Review of Systems section below for a description of possibly related adverse events and further discussion.

1.6.5. Fibrinolytic System

The renin-angiotensin system appears to play a role in regulating fibrinolysis as summarized in Section I.E.5 of this review. Measures of activity of the fibrinolytic system, plasminogen activator inhibitor-1 (PAI-1) or tissue plasminogen activator (t-PA), were measured in five studies. Both factors were measured in Studies 017, 021, and 022, and PAI-1 alone was measured in Studies 016 and 026. Units for all measurements were ng/ml except for Study 016, for which the PAI units were U/ml with a normal range of 1 to 14.99. Baseline values were mean 31.2 and median 24.5 ng/ml and mean 13.9 and median 10.5 U/l for PAI-1 and mean 12.4 and median 11.5 ng/ml for t-PA. None of these studies was placebo-controlled. Because HCTZ and amlodipine could be added to the treatment regimen after 8 weeks in Studies 017 and 021, only the values at 8 weeks for those studies are analyzed here.

Median changes in PAI-1 levels with eplerenone were positive for all studies, ranging from 2 to 20 percent. t-PA also showed median increases with eplerenone ranging from 1 to 19 percent. Changes with enalapril were varied for both factors, ranging from –11 to 14 percent for PAI-1 and from –1 to 4 percent for t-PA. Changes in PAI-1 with amlodipine were –2 and +6 percent.

If all studies that used the ng/ml units are combined, then the changes are shown in the tables below.

Table 45: Changes from Baseline in PAI-1 in Studies 017, 021, 022, and 026

Treatment	Mean	Median	Median %
amlodipine	-0.6	0.5	2.3%
eplerenone	2.9	3.1	13.0%
enalapril	-3.7	-2.7	-9.6%
combined	-1.8	0.2	0.7%

combined = eplerenone + enalapril

Table 46: Changes from Baseline in t-PA in Studies 017, 021, and 022

Treatment	Mean	Median	Median %
Amlodipine	-0.4	-0.4	-3.7%
Eplerenone	0.5	0.5	4.8%
Enalapril	0.8	0.5	4.5%
Combined	1.5	0.5	4.0%

combined = eplerenone + enalapril

Of the changes in the table above, only the PAI-1 change with eplerenone is significant ($p = 0.01$) by the signed ranks test. In Study 016 eplerenone produced about a 19 percent median increase in PAI-1 from baseline but enalapril produced about a 14 percent increase. Both of these changes are highly statistically significant.

Reviewer's comment: The results suggest that eplerenone alone produces a modest increase in PAI-1 and possibly a slight increase in t-PA. While the clinical significance of such changes is unclear, they do suggest a potential mechanism to explain any thrombotic adverse events with eplerenone.

1.7. Vital Signs

Changes in heart rate in the trials were small and not clinically significant. In the combined controlled trials, the mean heart rate change from baseline to final was +0.3 for the placebo groups, +0.4 for the eplerenone monotherapy groups, +0.2 for the coadministration groups, and +0.5 for the active control groups. The incidence of extreme heart rates was also similar across these treatment groups. The sponsor defined extreme heart rates as a 25 percent or greater deviation from baseline. The incidence of low extreme heart rate values was 1.6% in the placebo group, 1.0% in the eplerenone monotherapy group, 1.0% in the eplerenone coadministration therapy group, and 1.3% in the active comparator group. The incidence of high extreme heart rate values was 4.5% in the placebo group, 3.6% in the eplerenone monotherapy group, 3.0% in the eplerenone coadministration therapy group, and 3.9% in the active comparator group.

Body weight was collected at baseline and the final visit in Studies 010, 015, and 049 and every two to three weeks in Study 021. Study 021 was conducted in type 2 diabetic patients with microalbuminuria. The mean changes were a slight weight loss in the

groups treated with eplerenone (-0.6 kg for monotherapy and –0.7 kg for coadministration) and a slight weight gain for enalapril alone (+0.5 kg). No significant differences were observed between the eplerenone and eplerenone/enalapril treatment groups or between the enalapril and eplerenone/enalapril treatment groups for the incidence of extreme low or high body weight values defined as a change of greater than 5 percent from baseline. Mean changes from baseline to the final visit in body weight for Studies 010, 015, and 049 showed no clinically important differences among the placebo, eplerenone monotherapy, eplerenone coadministration therapy, and active comparator treatment groups. The changes in body weight observed in each group were small (range: -1.21 to 0.97). Analyses of extreme body weight values for Studies 010, 015, and 049 showed no clear trends among the treatment groups.

Reviewer's comment: Eplerenone does not appear to have clinically significant effects upon heart rate or body weight.

1.8. ECGs

The approach to monitoring ECGs was fairly uniform among the studies. Twelve-lead ECGs were required by protocol to be performed at screening or prior to randomization and at the final visit. (Some studies required ECGs at other times as well.) Many studies included the following inclusion criterion: "The patient had an ECG without clinically significant arrhythmia requiring treatment." The investigator was to interpret the ECGs and classify them as normal, abnormal not clinically significant, or abnormal clinically significant. The investigator also judged whether any ECG changes were adverse events.

The sponsor's summary of the ECG changes from baseline to final for all trials shown in the figure below.

Treatment Group	Baseline ECG Value	N	Final ECG Value: Normal	Abnormal NCS	Abnormal CS	Not Done
Placebo	NORMAL	30	25 (83.3)	5 (16.7)	0 (0.0)	0 (0.0)
	ABNORMAL NCS	20	1 (5.0)	18 (90.0)	0 (0.0)	1 (5.0)
	ABNORMAL CS	1	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)
	NOT DONE	314	266 (84.7)	132 (41.7)	4 (1.2)	19 (5.9)
Eplerenone Monotherapy	NORMAL	181	136 (74.0)	23 (12.7)	1 (0.6)	23 (10.7)
	ABNORMAL NCS	125	23 (18.4)	86 (68.8)	0 (0.0)	14 (11.2)
	NOT DONE	1442	802 (55.6)	466 (32.7)	11 (0.8)	143 (9.9)
Eplerenone Co-Admin Therapy	NORMAL	185	156 (84.3)	23 (12.4)	0 (0.0)	6 (3.2)
	ABNORMAL NCS	101	26 (25.5)	67 (71.9)	2 (1.7)	6 (5.0)
	NOT DONE	466	261 (56.0)	136 (29.6)	2 (0.4)	85 (13.9)
Active Comparators	NORMAL	146	105 (71.9)	7 (4.8)	0 (0.0)	34 (23.3)
	ABNORMAL NCS	103	14 (13.5)	69 (67.0)	0 (0.0)	19 (17.5)
	ABNORMAL CS	1	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)
	NOT DONE	1172	718 (61.0)	308 (26.3)	10 (0.9)	136 (11.9)

NCS = Not Clinically Significant; CS = Clinically Significant (as judged by investigator)

Figure 46: Sponsor's Changes in ECGs from Baseline for All Trials

While the results above do not suggest any detrimental effects of eplerenone upon ECGs, they have some limitations. Note that information on baseline ECGs is lacking for 78 percent of cases. The investigator's unguided classification of ECGs into three categories

would be expected to be highly variable. It is also not revealing as to the specific nature of the effects.

The sponsor's other tabulations of the resting 12-lead ECGs from the clinical trials are also not revealing. The sponsor provided two other types of analyses that are more informative: (1) detailed analyses of the ECG data from the phase I studies, including effects upon ECG intervals such as QTc; (2) detailed analyses of 24-hour Holter monitoring done in association with Study 026. These results are summarized below.

The five pharmacokinetic trials provided ECG data from 147 subjects (110 males and 37 females). The first trial (Study 001) was an active- and placebo-controlled, parallel-group, single rising dose tolerance study that evaluated eplerenone from 10 to 1000 mg compared to placebo and spironolactone. The other four trials were all multiple-dose, steady-state drug interaction studies that used cross-over designs. ECGs collected in the cisapride (Study 038) and erythromycin (Study 042) studies were each evaluated due to the common metabolic pathway shared with eplerenone, principally via the CYP3A4 isozyme. ECGs collected in the studies of digoxin, a cardiac glycoside (Study 007), and verapamil, a potent calcium channel blocker (Study 031), were evaluated due to their known affects on cardiac electrophysiology. More detail on these studies is provided in the figure below.

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Protocol No.: **Report No.:** **Short title:**	**Study Design:** **Study Population**	**Treatment** **No Randomized (N [Completed])** **Treatment Duration**
EE3-96-02-001 EE3-01-06-001 (16) Single dose tolerability and PK study	Phase I, single center, double-blind, randomized, placebo-controlled, single-dose parallel-group Healthy adult males N = 57 Aged 19 to 49 years	Eplerenone QD 10 mg (N = 8 [8]) 50 mg (N = 8 [8]) 100 mg (N = 8 [8]) 300 mg (N = 9 [8]) 1000 mg (N = 8 [8]) Spironolactone QD 50 mg (N = 8 [8]) Placebo QD (N = 8 [8]) Single Dose
NE3-99-02-007 NE3-01-06-007 (17) Digoxin Interaction PK Study	Single-center, open-label, randomized multiple-dose, three-period crossover Healthy young adults 12 females/12 males Aged 19 to 45 years	Eplerenone QD 100 mg (N = 24 [24]) Digoxin QD 200 µg (N = 24 [24]) Eplerenone QD plus Digoxin 100 mg /200 µg (N = 24 [24]) 10 days for each treatment period; treatment periods were separated by a 10-day washout period
NE3-00-02-031 NE3-01-06-031 (18) Verapamil HCl Interaction PK Study	Single-center, open-label, randomized, multiple-dose, three-period crossover Healthy young adults N = 24* 9 females/15 males Aged 19 to 44 years	Eplerenone QD 100 mg (N = 24 [24]) Verapamil QD 240 mg (N = 24 [24]) Eplerenone QD plus Verapamil QD 100 mg/240 mg (N = 24 [24]) 7 days for each treatment period, each period separated by a one-day washout period
NE3-99-02-038 NE3-01-06-038 (19) Cisapride Interaction PK study	Single- center open-label, randomized, multiple-dose, six-sequence, three-period crossover study. Healthy young adults N = 18* 10 females/8 males Aged 20 to 44 years	Eplerenone QD 100 mg (N = 18 [18]) Cisapride BID/QD 20 mg (N = 18 [18])* Eplerenone QD plus Cisapride BID/QD 100 mg/20 mg (N = 18 [18])* 6 days for each treatment period *QD dosing on Day 6 of each treatment period; treatment periods were separated by a two-day washout period
NE3-00-02-042 NE3-01-06-042 (20) Erythromycin Interaction PK study	Single-center, single-blind, randomized, multiple-dose, six-sequence, three-period crossover study. Healthy young adults N = 24 6 females/18 males Aged 21 to 44 years	Eplerenone QD 100 mg (N = 24 [24]) Erythromycin QD 500 mg QD (N = 24 [24]) Eplerenone QD plus Erythromycin BID 100 mg/500 mg (N = 24 [24]) 7 days for each treatment period, treatment periods were separated by a one-day washout period.

Figure 47: Sponsor's Summary of PK Studies with ECG Data

Study 001 did not show any clinically significant changes in any ECG parameters. No particular pattern of change in ECG parameters was noted with increasing eplerenone dose. The mean change from baseline in ECG parameters is shown in the figure below. Mean change from baseline between 30 msec and 60 msec in QTC intervals was observed in one subject while on eplerenone 10 mg and one subject while on eplerenone 50 mg group.

In Study 007, the 10-day digoxin interaction study, all groups showed a significant decrease in heart rate at day 10. For eplerenone 100 mg QD, the mean decrease was -3.5 bpm. QTc using Bazett's formula also decreased significantly, -8.2 msec for the eplerenone group. In Study 031, single dose with verapamil, all groups also showed a significant decrease in heart rate, -6.32 for eplerenone 100 mg. Verapamil showed the expected effect of prolongation of the PR interval; eplerenone did not show such an effect. In Study 038, the 6-7 day cisapride interaction study, all groups showed an increase in heart rate, +6.72 for eplerenone 100 mg QD. Cisapride showed a slight increase in QTc. The sponsor's summary of the results from Study 038 are shown in the figure below.

Parameter	Placebo	Eplerenone					Spiron
	N = 8	10 mg N = 8	50 mg N = 8	100 mg N = 8	300 mg N = 9	1000 mg N = 8	50 mg N = 8
HR (bpm)	-1.79 ± 2.23	-5.96 ± 0.65[b]	0.71 ± 1.50	1.33 ± 1.33	-2.04 ± 2.54	0.25 ± 2.35	-6.04 3.50
PR (msec)	-9.46 ± 4.29	-0.42 ± 2.54	4.29 ± 5.30	-4.33 ± 3.14	-1.22 ± 3.79	0.75 ± 2.46	-4.00 ± 5.81
QRS (msec)	4.00 ± 2.05	0.71± 2.14	-0.79 ± 1.62	-0.17 ± 2.02	0.67 ± 0.98	0.08 ± 1.68	3.21 ± 1.91
QT (msec)	-3.96 ± 7.84	9.54 ±3.03[a]	-2.17 ± 7.36	-14.25 ± 6.57	-3.11 ± 5.22	-7.62 ± 5.94	-6.17 ± 5.27
QTc[c] (msec)	-8.13 ± 2.53[b]	-3.12 ± 3.74	-0.37 ± 4.34	-10.79 ± 5.24[a]	-7.07 ± 3.29	-7.13 ± 2.48[a]	-17.88 ± 6.54[a]
QTc[d] (msec)	-10.04 ± 2.00[b]	-8.83 ± 4.25	0.88 ± 3.46	-9.08 ± 5.15	-8.63 ± 4.65	-7.04 ± 3.04	-23.71 ± 9.21[a]
MaxQTc[c] (msec)[a]	1.38 ± 3.40	10.63 ± 6.42	6.63 ± 5.89	-2.13 ± 5.54	-0.33 ± 4.11	-0.25 ± 2.93	-12.75 ± 5.96
MaxQTc[d] (msec)[a]	2.63 ± 2.04	5.88 ± 7.42	10.00 ± 5.11	0.25 ± 5.68	-0.22 ± 5.84	4.00 ± 4.04	-14.38 ± 9.12

Source: Final Report NE3-01-07-823, Appendix 1, Table 4
a indicates statistically significant difference in mean change from Baseline across treatments
b indicates statistically significant change from Baseline, $p < 0.05$
c calculated using Fridericia's formula
d calculated using Bazett's formula
MAX=mean maximum change from Baseline

Figure 48: Sponsor's Mean Change in Baseline for ECG Parameters for Study 038

Parameter	Cisapride 20 mg BID/QD mean ± SEM N = 18	Eplerenone 100 mg QD mean ± SEM N = 18	Cisapride 20 mg BID/QD + Eplerenone 100 mg QD mean ± SEM N = 18	P-Value[a]
HR (bpm)	6.82 ± 0.99[b]	6.72 ± 1.05[b]	9.32 ± 1.40[b]	0.008
PR (msec)	-5.69 ± 1.80[b]	-0.33 ± 1.69	-4.01 ± 2.39	0.000
QRS (msec)	-0.11 ± 0.78	0.14 ± 0.86	-0.38 ± 0.78	NS
QT (msec)	-12.81 ± 2.48[b]	-22.65 ± 2.79[b]	-15.15 ± 3.36[b]	0.001
QTc[c] (msec)	1.16 ± 1.76	-9.15 ± 1.43	3.70 ± 1.83	<0.001
QTc[d] (msec)	8.14 ± 2.23[b]	-2.33 ± 1.58[b]	13.29 ± 2.31[b]	<0.001
MaxQTc[c] (msec)	7.78 ± 2.23	-5.83 ± 1.93	6.17 ± 1.81	<0.001
MaxQTc[d] (msec)	18.50 ± 3.47[b]	1.83 ± 2.50	17.56 ± 3.41	<0.001

Source: Final Report NE3-01-07-823. Appendix 4, Table 4

a P-values < 0.05 indicates statistically significant difference in mean change from Baseline across treatments

b indicates statistically significant change from Baseline, p <0.05

c calculated using Fridericia's formula

d calculated using Bazett's formula

MAX=mean maximum change from Baseline

NS – not statistically significant across treatments

Figure 49: Sponsor's Mean Change in Baseline for ECG Parameters for Study 038

In Study 042, the erythromycin interaction study, each drug, when administered individually, resulted in a minor mean decrease in heart rate, though no such change was noted when the drugs were coadministered. When corrected for heart rate using either the Fridericia or Bazett method, the mean changes in QTc interval length indicated that neither erythromycin nor eplerenone had an effect on cardiac repolarization.

The sponsor's summary of the results of these studies is the following: "The results of the ECG analyses were uniform across the five studies and indicated that there was no effect of eplerenone on any of the analyzed ECG parameters, most notably the QTc interval. … the results of the studies suggest that eplerenone is devoid of ECG effects and does not indicate safety concerns in regard to cardiac repolarization effects."

Study 026 evaluated the effects of eplerenone versus amlodipine on ventricular repolarization and its associations with heart rate in patients with mild to moderate hypertension. Of the 179 patients randomized into this study, a total of 131 patients (58 eplerenone and 73 amlodipine) had two valid Holter recordings at the beginning of the single-blind placebo run-in period (Holter Baseline) and at Week 12 (Holter post-Baseline). QT- and RR-interval duration was measured in a total of 19827 complexes.

The sponsor's summary of the effects upon ECG parameters is the following:

"• There was no difference in the mean change from Baseline for the QT interval between eplerenone and amlodipine.

• Within the eplerenone group, no change from Baseline was observed for the QT, QTcB, QTcF, QTcr or RR-interval.

• No clinical meaningful mean change from Baseline in outliers in QT and QTcB and no clinical meaningful incidence of outliers in QTcB could be observed."

A tabulation of the effects on ECF parameters from these Holter data is shown in the figure below.

Variable	Eplerenone			Amlodipine		
Timepoint	0hr [msec]	1.5hr [msec]	3hr [msec]	0hr [msec]	1.5hr [msec]	3hr [msec]
ΔQT [msec] 95% CI	4.2 (-2.5,10.5)	-7.1 (-14.8,0.5)	-8.8* (-16.0,-1.6)	4.1 (-1.6,9.9)	-6.2 (-13.3,0.9)	-7.8* (-14.5,-1.2)
ΔRR [msec]	11.9	-33.7*	-38.5*	33.6*	-29.1	-33.4*
ΔQTcB [msec] 95% CI	1.3 (-4.3,6.8)	1.8 (-2.4,6.0)	0.1 (-4.5,4.6)	-4.0 (-9.1,1.1)	1.0 (-2.9,4.9)	-0.1 (-4.2,4.1)
ΔQTcF [msec] 95% CI	2.3 (-2.2,6.9)	-1.5 (-5.6,2.6)	-3.2 (-7.3,0.9)	-1.0 (-5.1,3.2)	-1.7 (-5.5,2.1)	-2.8 (-6.6,0.9)
ΔQTcr [msec] 95% CI	-3.2 (-10.7,6.0)	-4.8 (-12.9,3.2)	1.9 (-7.6,11.5)	1.0 (-6.6,8.6)	-1.1 (-8.6,6.4)	-2.8 (-11.7,6.0)

Source: Study 026
* Significant at the 5% level

Figure 50: Sponsor's Changes in ECG Parameters from Holter Data in Study 026

Study 026 also included arrhythmia analyses using the Holter data. The results are tabulated below. There were no significant differences between the amlodipine and eplerenone groups.

Arrhythmia	Eplerenone 50-200 mg QD		Amlodipine 2.5-10 mg QD	
No. treated	58		73	
Any arrhythmia	19	(32.8)	26	(35.6)
Isolated VE's showing the R and T phenomenon	0	(0.0)	1	(1.4)
Atrial fibrillation or flutter	2	(3.4)	1	(1.4)
Ventricular tachycardia regardless of rate (defined as three ectopic beats in a row)	3	(5.2)	6	(8.2)
Presence of IVCD or Bundle Branch Block	9	(15.5)	6	(8.2)
Transient or fixed 2nd degree or 3rd degree AV block	1	(1.7)	0	(0.0)
Ventricular asystole or sinus pauses greater than or equal to 2.0 seconds	1	(1.7)	3	(4.1)
Any SVT at a rate of 180 bpm or greater; or 10 or more beats in a row	10	(17.2)	9	(12.3)
Multiform or uniform ventricular ectopics greater than 100/hour in any hour	1	(1.7)	7	(9.6)

Source: Table T18.
Includes Study 026.
Data are expressed as N (% of patients) except for No. treated.
Note: No significant differences were observed between the treatment groups.

Figure 51: Sponsor's Arrhythmia Analysis (Study 026)

The reviewer also examined the reports of ECG abnormalities classified as adverse events. Such ECG AEs were infrequent and not more common in the eplerenone groups. They typically were ST or T wave abnormalities suggestive of ischemia or ventricular strain. Note that frank arrhythmias or severe ischemic changes, i.e., unstable angina or myocardial infarction, were coded to the more specific AE categories.

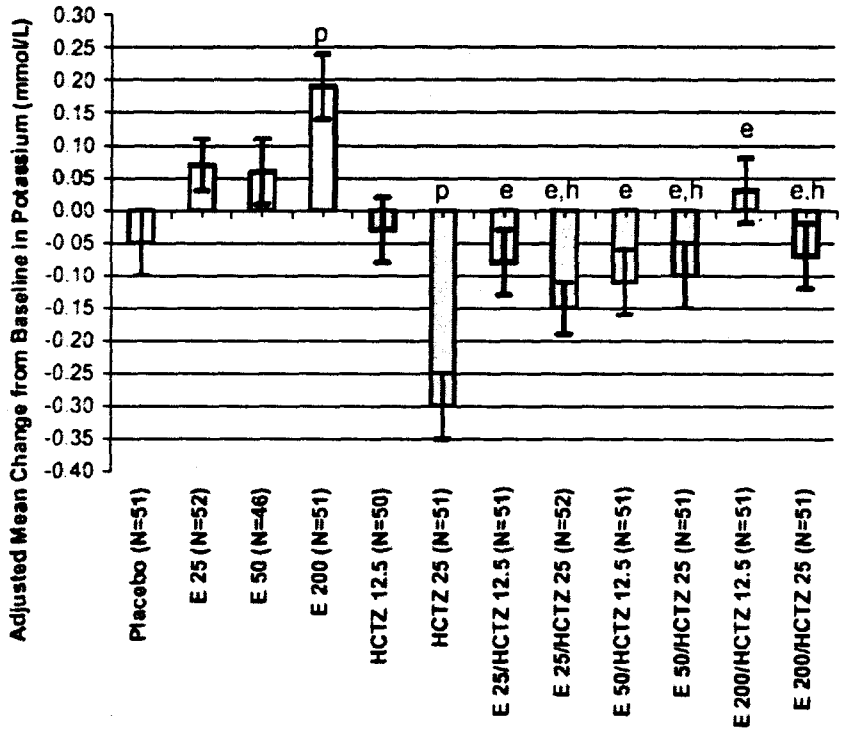
Reviewer's comment: The ECG data do not indicate that eplerenone has a significant effect upon ventricular repolarization or other ECG parameters. The one limitation is that the ECGs on the vast majority of patients in the clinical trials were minimally reported and provide little useful information.

1.9. Special Studies

Effects of eplerenone upon sex hormones are discussed in the laboratory values section. Effects of eplerenone on renin-angiotensin systems hormones are discussed in the secondary efficacy sections. Eplerenone was used with other antihypertensive medications in many studies, and the toxicities of the combinations are summarized here.

Hydrochlorothiazide (HCTZ)

Study 015, a dose ranging factorial study of eplerenone and HCTZ, is the only study with defined eplerenone-HCTZ arms. HCTZ add-on to control BP was specified in three trials (019, 017, and 021) and permitted in Study 025. Study 015 had arms crossing eplerenone dosages of 25, 50, and 200 mg with HCTZ 12.5 and 25 mg as well as monotherapy and placebo arms. The combinations of eplerenone and HCTZ were well-tolerated in this study. Nausea led to withdrawal in four and vomiting was reported in two combination arm patients, but otherwise the AEs were similar between all active treatment arms. Hyperkalemia was not a clinical problem in this study. The combinations produced small decreases in mean potassium levels as opposed to the increases seen with eplerenone monotherapy. The potassium changes are shown in the figure below.



p=statistically significantly different from placebo ($p < 0.001$).
e=statistically significantly different from corresponding eplerenone monotherapy ($p \leq 0.019$).
h=statistically significantly different from corresponding HCTZ monotherapy ($p \leq 0.017$).
E=eplerenone, HCTZ=hydrochlorothiazide

(Figure 10.a)

Figure 52: Sponsor's Adjusted Mean Change from Baseline to the Final Visit in Serum Potassium

β Blockers (BBs)

Eplerenone titrated 50-100 mg was added for eight weeks to a BB in 135 patients not completely controlled on their usual dosages of unspecified BBs in Study 024. The combination was very well tolerated with similar AE rates between the two arms. The most common AEs were headache (7.6 percent placebo, 2.9 percent eplerenone), influenza-like symptoms (6.1 percent placebo, 0.0 percent eplerenone), and hyperkalemia (0 percent placebo, 5.8 percent eplerenone). One eplerenone patient was prematurely discontinued from the study due to an adverse event of hyperkalemia (5.7 mmol/L) that occurred after 17 days of treatment. Three other eplerenone patients also experienced hyperkalemia.

Calcium Channel Blockers (CCBs)

Eplerenone titrated 50-100 mg was also added for eight weeks to a CCB in 137 patients not completely controlled on their usual dosages of unspecified CCBs in Study 024. Total AEs were slightly more common with the addition of eplerenone (27.1 vs 22.4 percent). The most common AEs headache (3.0 percent placebo, 7.1 percent eplerenone) and nausea (0 percent placebo, 5.7 percent eplerenone). There were no hyperkalemia AEs. Four (5.7 percent) eplerenone patients were prematurely withdrawn from the study due to at least one treatment-emergent adverse event. The AEs were varied (aortic aneurysm, heart failure, scotoma, fatigue/dizziness). The combination of eplerenone with a CCB appears to be well tolerated overall.

ACE Inhibitors (ACEIs)

Eplerenone titrated 50-100 mg was added for eight weeks to an ACEI in 177 patients not completely controlled on their usual dosages of unspecified ACEIs in Study 023. The combination arm was well-tolerated with AE rates similar to the ACEI-placebo arm. The most common treatment-emergent AEs were headache (13 percent placebo, 16 percent eplerenone) and dizziness (1.1 percent placebo, 5.7 percent eplerenone). One patient in the eplerenone-ACEI arm had a mild (5.5 meq/L) hyperkalemia AE that returned to normal by the end of the study. Mean change in potassium levels did not differ between the two groups. There were no reports of gynecomastia or menstrual abnormalities.

Enalapril was compared to and combined with the ACEI enalapril in two studies with non-BP primary endpoints: Study 017 in hypertensive patients with left ventricular hypertrophy and a primary endpoint of change in left ventricular mass and Study 021 in hypertensive diabetics with albuminuria and a primary endpoint of change in albuminuria. In both studies patients were randomized to eplerenone forced-titrated 50-200 mg QD over four weeks, enalapril forced-titrated 10 to 40 mg QD, or eplerenone forced-titrated over four weeks plus fixed enalapril 10 mg QD. HCTZ 12.5-25 mg and then amlodipine 10 mg could be added after eight weeks to control BP if necessary. Study 017 randomized 202 patients and had a study duration of 36 weeks while Study

021 randomized 266 patients and had a study duration of 24 weeks. The most notable safety finding for these studies is the high rates of hyperkalemia in Study 021: 16 percent in the eplerenone arm and 24 percent in the combined arm vs. 6 percent in the enalapril arm. Six eplerenone and 13 combined vs. 2 enalapril patients were withdrawn because of hyperkalemia. This study permitted the enrollment of patients with mild renal dysfunction (creatinine to 1.7 mg/dL). The sponsor noted an association between lower creatinine clearance and more hyperkalemia.

Angiotensin Receptor Blockers (ARBs)

Eplerenone titrated 50-100 mg was added to an ARB for eight weeks in 164 patients not completely controlled on their usual dosages of unspecified ACEIs in Study 023. The combination arm was well-tolerated with AE rates similar to the ARB-placebo arm. The most common AEs were headache (20 percent placebo, 23 percent eplerenone), nausea (4.9 percent placebo, 9.6 percent eplerenone), polyuria (6.2 percent placebo, 4.8 percent eplerenone), and asthenia (11 percent placebo, 2.4 percent eplerenone). No patients had hyperkalemia AEs. The eplerenone-ARB group did have a statistically significant increase in mean potassium levels (0.13 vs 0.03 meq/L, p = 0.0083). There were no reports of gynecomastia or menstrual abnormalities, although one eplerenone-ARB patient had orchitis and a severe headache.

1.10. Withdrawal Phenomena/Abuse Potential

The sponsor's summary of studies of withdrawal effects is the following: "Studies 020, 021, 022, 023, 024, and 026 had a scheduled safety visit approximately one week after the final treatment visit. This one-week interval provided a timeframe during which rebound phenomenon was examined. Summaries of rebound SBP, DBP, and heart rate were prepared for all completer patients and completer patients with no antihypertensive medication between the final and safety visit. The incidence of patients who exhibited a 15 mmHg drop from Baseline to the final visit in SBP that subsequently increased 5 mmHg above the original Baseline value at the safety visit was similar between the placebo (2.3%), eplerenone monotherapy (2.3%), eplerenone coadministration therapy (2.7%), and active comparator (2.2%) treatment groups; no antihypertensive medication was administered to these patients between the final visit and the safety visit... Among patients who did not receive antihypertensive medication between the final visit and the safety visit, the mean change from the final visit to the safety visit in SBP was 3.3 mmHg in the placebo group, 6.5 mmHg in the eplerenone monotherapy group, 6.2 mmHg in the eplerenone coadministration therapy group, and 5.2 mmHg in the active comparator group... The incidence of adverse events reported during this period was similar among the placebo, eplerenone monotherapy, eplerenone coadministration therapy, and active comparator treatment groups."

No cases of abuse were mentioned in the NDA.

Reviewer's comment: Eplerenone does not appear to cause withdrawal or rebound problems. Eplerenone would appear to have minimal abuse potential.

1.11. Human Reproduction Data

The sponsor's description of one pregnancy in a study patient is the following: "The eplerenone clinical development program required patients to be post-menopausal, surgically sterile, or using barrier or hormonal contraceptives. However, one patient in Study 019 became pregnant while receiving eplerenone in the trial. The patient was 23 years old and had a diagnosis of low-renin hypertension. The patient was prematurely discontinued from the study on October 5, 2000, after having received 99 days of treatment with eplerenone, when she was noted to be pregnant. The patient was hospitalized twice during the pregnancy, once due to fluid retention and once due to pre-eclampsia. The patient delivered a healthy 2.8 kg male of 37 weeks gestation on 9 May 2001. Apgar scores were 8 at one minute, 10 at five minutes, and 10 at 10 minutes. Subsequent testing of the infant revealed no anomalies and a normal rate of growth."

1.12. Overdose Experience

No overdoses have been reported in the clinical program.

2. Review of Systems

2.1. Cardiovascular

Serious or withdrawal-causing cardiovascular event rates did not appear to differ among the treatment groups. Cerebrovascular AEs causing withdrawal were slightly more common in the eplerenone groups but the rates were low and not statistically significantly different. The reviewer examined the rates for all cardiovascular AEs in the following categories: cerebrovascular accidents, coronary artery-related events (myocardial infarction and angina combined and separately), and peripheral vascular thromboses or thrombophlebitis (arterial, venous, and combined.) The rates by treatment group are shown in the table below.

Table 47: Reviewer's Cardiovascular AE Rates

Group	Cerebro-Vascular		Coronary Artery Disease						Peripheral Vascular Thrombosis					
			Any		MI		Angina		Any		Venous		Arterial	
	%	/PEY	%	/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														

SL = Spironolactone; MI = myocardial infarction; /PEY = per 100 patient exposure years

The rates for these cardiovascular AEs, with the exception of MIs, are highest in the eplerenone monotherapy group. However, the rate differences are not statistically significant.

The ECG data do not indicate that eplerenone has a significant effect upon ventricular repolarization or other ECG parameters. The rates of reported arrhythmia AEs is shown in the table below.

Table 48: Reviewer's Rates of Arrhythmia AEs

Group	Any		Ventricular	
	%	/100 PEY	%	/100 PEY
Active	1.2%	3.9	0.2%	0.7
Coadmin	1.0%	5.3	0.4%	2.0
Monotherapy	0.9%	2.9	0.2%	0.6
Open label	1.2%	2.7	0.2%	0.4
Placebo	0.3%	1.3	0.0%	0.0
Spironolactone	0.8%	3.6	0.0%	0.0

The rates were highest in the coadministration groups and second highest in the active control groups. Eplerenone does not appear to cause more arrhythmias than active controls.

2.2. Gastrointestinal

Liver Function

From the analyses of liver function tests, eplerenone appears to produce a slight, statistically significant, dose-related increases in ALT and GGT. This effect may produce a slight increase in moderate elevations in these enzymes.

One subject in a PK study in healthy Japanese subjects (conducted in the U.S.) developed liver enzyme elevations. After seven days of treatment with eplerenone 100 mg daily

ALT was elevated 13-fold and AST and GGT 5-6 fold in one 44-year old male subject. Twenty-eight days after treatment ALT and AST were normal but GGT remained slightly elevated, testing normal 61 days after treatment. He had demonstrated similar enzyme increases during a previous placebo-controlled study. The subject was challenged with a high caloric diet (3500 calories per day) and with a weight maintenance diet (2000 calories per day.) During challenge with the high caloric diet he experienced enzyme elevations similar to those during the eplerenone treatment. He remained asymptomatic throughout these studies. Another subject in a PK study also developed liver enzyme elevations that were attributed to a change in hepatitis C reactivity from negative to positive.

The sponsor's summary of hepatic adverse events from the combined controlled trials is shown in the figure below. The reported hepatic adverse events were enzyme elevations consistent with the analyses of changes in the laboratory values.

Adverse Event	Placebo		Eplerenone Monotherapy		Eplerenone Coadministration Therapy		Active Comparators	
No. treated	375		1748		772		1422	
Any event	5	(1.3)	36	(2.1)	12	(1.6)	24	(1.7)
Increased GGT	2	(0.5)	22	(1.3)	5	(0.6)	12	(0.8)
Phosphatase alkaline increased	1	(0.3)	8	(0.5)	0	(0.0)	4	(0.3)
SGOT increased	2	(0.5)	13	(0.7)	3	(0.4)	11	(0.8)
SGPT increased	3	(0.8)	20	(1.1)	4	(0.5)	13	(0.9)

Source: Table T34.1.1.1
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 026, and 049, no additional antihypertensive medication data included (Table 12.e)

Figure 53: Sponsor's Hepatic Adverse Events with Incidence >= 0.5% in Any Treatment Group, Combined Controlled Trials

Two eplerenone patients had hepatic SAEs. One patient was a 60 year-old white female who had an episode of cholecystitis while being treated with eplerenone 200 mg QD and hydrochlorothiazide 25 mg QD in Study 025. Her medications were continued during the episode, which resolved in one week, and for 40 days until study termination. The sponsor's summary of the other patient is included below:

"Study 021: Patient # GE4912-07212692 (SGOT increased, SGPT increased, increased GGT, and nausea), was a 60-year-old Caucasian male with a history of carcinoma of larynx, cataracts (left and right eyes), erectile dysfunction, albuminuria, arthrosis of spine, active diabetes type 2, and high GGT level (115 U/L). He received his first dose of eplerenone 50 mg QD on 14 Jul 2000 (Baseline). Study medication was increased to eplerenone 100 mg on 27 Jul 2000 (Day 14) and increased to eplerenone 200 mg on 17 Aug 2000 (Day 35). Hydrochlorothiazide 25 mg QD and amlodipine 10 mg QD were added to his regimen on 05 Oct 2000 (Day 84); his final dose of study medication was on