PRODUCT MONOGRAPH

[Pr]MINT-EPLERENONE

Eplerenone Tablets

25 mg and 50 mg

Aldosterone Antagonist

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets 25 mg, 50 mg	Croscarmellose sodium, D&C Yellow #10 Aluminium Lake, FD&C Yellow #6 Aluminimum lake, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, lactose monohydrate, polyethylene glycol, magnesium stearate, microcrystalline cellulose, polysorbate 80, sodium lauryl sulfate, talc, titanium dioxide.

INDICATIONS AND CLINICAL USE

MINT-EPLERENONE (eplerenone) is indicated as an adjunct to standard therapy to reduce the risk of cardiovascular mortality and hospitalization for heart failure in patients with NYHA class II systolic chronic heart failure and left ventricular systolic dysfunction. In patients 75 years and older a reduction in cardiovascular mortality was not observed with eplerenone (see WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics, and CLINICAL TRIALS – EMHASIS-HF Study).

MINT-EPLERENONE (eplerenone) is indicated as an adjunct to standard therapy to reduce the risk of mortality and hospitalization for heart failure following myocardial infarction in clinically stable adult patients who have evidence of heart failure and left ventricular systolic dysfunction (ejection fraction ≤40%). In patients 75 years and older a reduction in mortality was not observed with eplerenone (see WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics, and CLINICAL TRIALS – EPHESUS Study).

MINT-EPLERENONE (eplerenone) is indicated for the treatment of mild and moderate essential hypertension, usually in combination with other drugs, for patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate.

Serum potassium level should be measured and glomerular filtration rate should be estimated before starting MINT-EPLERENONE therapy and MINT-EPLERENONE should not be

administered if initial serum potassium is >5.0 mmol/L or if estimated glomerular filtration rate is <30 mL/min/1.73m^2 (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

MINT-EPLERENONE (eplerenone) is contraindicated in all patients with the following:

- hypersensitivity to eplerenone or any component of this medication (for a complete listing of the MINT-EPLERENONE components, see DOSAGE FORMS, COMPOSITION AND PACKAGING);
- patients with clinically significant hyperkalemia;
- severe hepatic impairment (Child-Pugh Class C);
- serum potassium >5.0 mmol/L at initiation;
- severe renal impairment [eGFR <30 mL/min/1.73 m^2];
- concomitant use with potassium-sparing diuretics, potassium supplements or strong CYP3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, telithromycin, clarithromycin, ritonavir, and nelfinavir (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

MINT-EPLERENONE (eplerenone) is also contraindicated for the treatment of hypertension in patients with:

- type 2 diabetes with microalbuminuria
- serum creatinine >132 µmol/L in males or >115 µmol/L in females
- moderate to severe renal impairment [eGFR<50 mL/min/1.73 m^2]

WARNINGS AND PRECAUTIONS

Hyperkalemia

The principal risk of MINT-EPLERENONE (eplerenone) is hyperkalemia. Hyperkalemia, if not recognized in a timely manner, can cause serious, sometimes fatal, arrhythmias. All patients prescribed MINT-EPLERENONE must have their serum potassium level measured before initiating MINT-EPLERENONE therapy, within one week and at one month after the first dose or after a dose adjustment, and measured periodically thereafter, as clinically warranted (see DOSAGE AND ADMINISTRATION).

Hyperkalemia can be minimized by appropriate patient selection, avoidance of certain concomitant treatments, thoroughly informing the patient and periodic monitoring until the effect of MINT-EPLERENONE has been established.

For patient selection and medications which should not be prescribed concomitantly with MINT-EPLERENONE or prescribed with caution, see CONTRAINDICATIONS, DRUG INTERACTIONS; and ADVERSE REACTIONS.

MINT-EPLERENONE should not be administered to heart failure patients with initial serum potassium >5.0 mmol/L, and/or eGFR <30 mL/min/1.73m^2. The incidence of hyperkalemia increases with declining renal function (see ADVERSE EVENTS, **Tables 6 and 9**).

MINT-EPLERENONE should not be administered to hypertensive patients with initial serum potassium >5.0 mmol/L, and/or eGFR <50 mL/min/1.73 m^2. In patients with hypertension who have reduced eGFR, serum potassium concentrations should be closely monitored when treated with MINT-EPLERENONE, especially when co-administrated with other antihypertensive drugs. Even in hypertensive patients with normal renal function, hyperkalemia may occur when treated with eplerenone (see ADVERSE REACTIONS, Table 11). Overdose is associated with a significantly increased frequency of hyperkalemia (serum potassium > 5.5 mmol/L).

Diabetic patients with heart failure (HF) who are treated with MINT-EPLERENONE, especially those with proteinuria or renal impairment, should also be treated with caution as they have an increased risk of hyperkalemia. Patients with either diabetes or renal impairment / proteinuria also have an increased risk of hyperkalemia, however the incidence remains lower than in patients with both of these comorbidities (see ADVERSE REACTIONS, Tables 7 and 10).

Impaired Hepatic Function
In 16 subjects with mild-to-moderate hepatic impairment (Child-Pugh Class B) who received 400 mg of eplerenone, no elevations of serum potassium above 5.5 mmol/L were observed. C_{max} was not significantly changed but AUC was increased by 42% and eplerenone clearance 30% lower compared to matched controls. The dose recommended is 8 times smaller and, therefore, no dose adjustment is necessary in patients with *mild to moderate* hepatic impairment.

The use of eplerenone in patients with severe hepatic impairment has not been evaluated and therefore, MINT-EPLERENONE is contraindicated in these patients (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Impaired Renal Function
See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Hyperkalemia, ADVERSE REACTIONS.

Carcinogenesis, Mutagenesis
Preclinical studies of safety pharmacology, genotoxicity, carcinogenic potential and toxicity to reproduction revealed no special hazard for humans.

In repeat dose toxicity studies, prostate atrophy was observed in rats and dogs at exposure levels several-fold above clinical exposure levels. The prostatic changes were not associated with adverse functional consequences. The clinical relevance of these findings is unknown.

Studies in rats and rabbits showed no teratogenic effects, although decreased body weight in maternal rabbits and increased rabbit fetal resorptions and post-implantation loss were observed at the highest administered dosage.

Special Populations

Pregnant Women
There are no eplerenone studies in pregnant women. Eplerenone did not impair fertility and was not teratogenic in animals but the risk to the fetus of pregnant women is not known. Therefore, MINT-EPLERENONE should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus (see TOXICOLOGY).

Nursing Women
It has not been determined if eplerenone is present in human breast milk, however it was present in rat breast milk at a milk to plasma ratio of 0.85. Because many drugs are excreted in human milk and because of the unknown potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see TOXICOLOGY).

Pediatrics

The safety and effectiveness of eplerenone have not been established in pediatric patients and MINT-EPLERENONE is not recommended in this patient population.

Geriatrics
There were 1641 (46%) patients treated with eplerenone in EPHESUS who were 65 and over, while 616 (18.6%) were 75 and over. Patients greater than 75 years did not appear to benefit from the use of eplerenone (see CLINICAL TRIALS – EPHESUS study).

There were 1854 (68%) patients treated with eplerenone in EMPHASIS-HF who were 65 years and over, while 657 (24%) were 75 years and over. Both subgroups of patients appeared to benefit from the use of eplerenone compared to placebo-treated patients, based on the results from the primary endpoint (composite endpoint CV mortality or hospitalization for heart failure) but these results were driven by a significant reduction of hospitalization for heart failure. While hospitalization for heart failure was reduced in all age groups, the study did not show a reduction in cardiovascular mortality with eplerenone in patients 75 years and older (see CLINICAL TRIALS – EMPHASIS-HF study).

Of the patients treated with eplerenone in hypertension studies, 629 (22%) were 65 years old and over, and 104 (3.7%) were 75 years old and over. No differences in safety or effectiveness were observed between elderly patients and younger subjects.

No initial dose adjustment is required in the elderly. Due to an age-related decline in renal function, the risk of hyperkalemia is increased in elderly patients. This risk may be further increased when co-morbidity associated with increased systemic exposure is also present, in particular mild-to-moderate hepatic impairment. Periodic monitoring of serum potassium is recommended.

ADVERSE REACTIONS

Clinical Trial Adverse Events

Because clinical trials are conducted under very specific conditions the adverse drug

reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

NYHA Class II Chronic Heart Failure

EMPHASIS-HF study: NYHA Class II chronic heart failure

In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), safety was evaluated in 1364 patients treated with eplerenone and followed-up for a median duration of 675 days, and 1372 placebo-treated patients, followed-up for a median of 615 days during the double-blind phase of the trial. All causality adverse events that occurred in ≥2% of subjects treated with eplerenone (also incidence higher than placebo) are presented in **Table 1.**

Table 1. Incidence of Adverse Events ≥ 2% of Subjects in the eplerenone arm and more frequent than placebo, in the EMPHASIS-HF Study.

Body System Adverse Event	Eplerenone 25-50 mg QD N=1364	Placebo N=1372	P-value†
Blood and Lymphatic System Disorders			
Anemia	32 (2.3%)	28 (2.0%)	-
Cardiac Disorders			
Myocardial infarction	36 (2.6%)	34 (2.5%)	-
Gastrointestinal Disorders			
Constipation	32 (2.3%)	15 (1.1%)	0.0123
Infections and Infestations			
Nasopharyngitis	49 (3.6%)	48 (3.5%)	-
Upper respiratory tract infection	39 (2.9%)	35 (2.6%)	-
Metabolism and Nutrition Disorders			
Diabetes mellitus	33 (2.4%)	28 (2.0%)	-
Hyperkalemia*	118 (8.7%)	55 (4.0%)	< 0.0001
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	30 (2.2%)	29 (2.1%)	-
Nervous System Disorders			
Dizziness	66 (4.8%)	65 (4.7%)	-
Headache	35 (2.6%)	32 (2.3%)	-
Syncope	37 (2.7%)	31 (2.3%)	-
Renal and Urinary Disorders			
Renal impairment	68 (5.0%)	44 (3.2%)	0.0205
Respiratory, Thoracic and Mediastinal Disorders			
Cough	57 (4.2%)	48 (3.5%)	-
Skin and Subcutaneous Tissue Disorders			
Pruritus	29 (2.1%)	15 (1.1%)	0.0338
Vascular Disorders			
Hypotension	55 (4.0%)	42 (3.1%)	-

* Judged as an adverse event by the investigator regardless of specific serum potassium value.

† A dash indicates no statistically significant difference between treatment groups (p>0.05).

The overall incidence of treatment-related adverse events reported with eplerenone versus placebo was 21.3% and 17.1%, respectively. The only treatment-related AE that occurred in 2% of subjects in either treatment group was hyperkalemia (7.0% in the eplerenone group vs 2.9% in the placebo group).

A total of 1272 subjects reported serious adverse events (SAE); 586 subjects (43.0%) in the eplerenone group and 686 subjects (50.0%) in the placebo group.

A total of 472 subjects discontinued from the study due to adverse events; 215 subjects (15.8%) in the eplerenone group and 257 subjects (18.7%) in the placebo group. A total of 32 subjects discontinued due to hyperkalemia; 19 subjects (1.4%) in the eplerenone group and 13 subjects (0.9%) in the placebo group.

A summary of the incidence of hyperkalemia and hypokalemia is provided in **Table 5**.

Heart Failure following Myocardial Infarction

EPHESUS study: Post-myocardial infarction heart failure

In the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS), safety was evaluated in 3307 patients treated with eplerenone and 3301 placebo-treated patients. Patients were followed for an average of 16 months (see CLINICAL TRIALS). Vital status was confirmed for 99.7% of patients.

The most serious adverse events in EPHESUS were endpoint events (e.g., death, cardiac failure) and these were significantly more frequent in the placebo treatment group. Serious adverse events that were significantly associated with eplerenone treatment included dehydration, arterial leg thrombosis, increased creatinine, and pyelonephritis; the incidence of these was low (0.5%).

Headache was the most frequent adverse reaction among eplerenone subjects in single- and multiple-dose trials**.** Adverse events that occurred more frequently in patients treated with eplerenone than placebo were hyperkalemia (summarized in **Table 7**). Eplerenone-treated patients also experienced more postural hypotension (0.7% vs 0.3% on placebo). Other adverse events more frequent during eplerenone treatment were increased blood urea nitrogen (BUN), increased creatinine, hypothyroidism, gastroesophageal reflux, pancreatitis, ketosis, arterial leg thrombosis, sepsis, and varicose veins. Hypokalemia (<3.5 mmol/l) occurred less frequently in patients treated with eplerenone (8.4% vs. 13.1%).

Elevation of serum potassium led to appropriate dose adjustments of eplerenone (see **Table 16**, Dose adjustment). Permanent discontinuations of eplerenone treatment due to hyperkalemia were infrequent (0.7% eplerenone vs 0.3% placebo); no eplerenone patient died from hyperkalemia. Sepsis led to permanent discontinuation of study medication in 2 eplerenone patients. No patients permanently discontinued study medication due to postural hypotension.

Adverse events experienced by ≥2.0% of subjects treated with eplerenone (also incidence

higher than placebo) are presented in **Table 2**.

Table 2. Incidence of Adverse Events ≥ 2% of Subjects in the eplerenone arm and more frequent than placebo, in the EPHESUS Study.

Body System Adverse Event	Eplerenone 25-50 mg QD N=3307	Placebo N=3301	P-value†
Autonomic Nervous System Disorders			
Hypotension	119 (3.6%)	109 (3.3%)	-
Syncope	71 (2.1%)	58 (1.8%)	-
Body as a Whole - General Disorders			
Asthenia	89 (2.7%)	68 (2.1%)	-
Chest Pain Non-Cardiac	213 (6.4%)	206 (6.2%)	-
Fatigue	95 (2.9%)	91 (2.8%)	-
Fever	67 (2.4%)	65 (2.0%)	-
Central and Peripheral Nervous System Disorders			
Dizziness	214 (6.5%)	197 (6.0%)	-
Headache	126 (3.8%)	119 (3.6%)	-
Gastrointestinal System Disorders			
Constipation	98 (3.0%)	92 (2.8%)	-
Diarrhea	115 (3.5%)	113 (3.4%)	-
Dyspepsia	129 (3.9%)	120 (3.6%)	-
Nausea	139 (4.2%)	133 (4.0%)	-
Vomiting	76 (2.3%)	59 (1.8%)	-
Heart Rate and Rhythm Disorders			
Tachycardia Ventricular	70 (2.1%)	63 (1.9%)	-
Metabolism and Nutritional Disorders			
Hyperkalemia	113 (3.4%)	66 (2.0%)	0.0005
Myo Endo Pericardial & Valve Disorders			
Angina Pectoris	459 (13.9%)	415 (12.6%)	-
Coronary Artery Disorder	100 (3.0%)	91 (2.8%)	-
Red Blood Cell Disorders			
Anemia	115 (3.5%)	98 (3.0%)	-
Urinary System Disorders			
Creatinine Increase	81 (2.4%)	51 (1.5%)	0.0105
Hematuria	70 (2.1%)	55 (1.7%)	-
Renal Function Abnormal	96 (2.9%)	79 (2.4%)	-
Vascular (Extracardiac) Disorders			
Cerebrovascular Disorder	103 (3.1%)	101 (3.1%)	-

† From Fisher's exact test. A dash indicates no statistically significant difference between treatment groups (p>0.05).

The incidences of sex hormone-related adverse events are shown in **Table 3**.

Table 3. Rates of Sex Hormone-Related Adverse Events in EPHESUS

	Rates in Males		Rates in Females
	Gynecomastia	Mastodynia	Abnormal Vaginal Bleeding
Eplerenone	0.4%	0.1%	0.4%
Placebo	0.5%	0.1%	0.4%

Hypertension:

Eplerenone has been evaluated for safety in 3,299 patients as either monotherapy or co-administration therapy in the hypertension clinical trials. A total of approximately 499 patients were treated with eplerenone for over 6 months and more than 176 patients were treated for over 1 year. The most commonly reported adverse events were headache (11.2%) and upper respiratory tract infection (7.6%).

In placebo-controlled fixed-dose trials, the overall rates of adverse events were 46% with recommended doses of eplerenone and 48% with placebo. Adverse events occurred at a similar rate regardless of age, gender, or race. Therapy was discontinued due to an adverse event in 2.5% of patients treated with eplerenone and 2.7% of patients given placebo.

The adverse events that were reported at a rate of at least 1% of patients and at a higher rate in patients treated with eplerenone versus placebo are shown in Table 4.

Table 4. Incidence of Adverse Events ≥1% of Subjects in the Eplerenone pooled arms and More Frequent than Placebo in the Placebo-Controlled Fixed-Dose Monotherapy Trials

	Placebo	Eplerenone		
		25 mg/day	50 mg/day	100 mg/day
Subjects	244	97	294	239
Body as a Whole – General disorders Edema peripheral Fatigue Influenza-like symptoms	 4 (1.6%) 1 (0.4%) 3 (1.2%)	 3 (3.1%) 1 (1.0%) 2 (2.1%)	 5 (1.7%) 4 (1.4%) 5 (1.7%)	 2 (0.8%) 2 (0.8%) 5 (2.1%)
Cardiovascular Disorders Palpitation	1 (0.4%)	1 (1.0%)	3 (1.0%)	3 (1.3%)
Central and Peripheral Nervous System Disorders Dizziness	5 (2.0%)	3 (3.1%)	8 (2.7%)	7 (2.9%)
Gastrointestinal System Disorders Abdominal pain	2 (0.8%)	3 (3.1%)	2 (0.7%)	4 (1.7%)
Liver and Biliary system Disorders Bilirubinemia Increased GGT SGOT increased SGPT increased	 0 2 (0.8%) 2 (0.8%) 1 (0.4%)	 0 1 (1.0%) 1 (1.0%) 1 (1.0%)	 1 (0.3%) 5 (1.7%) 4 (1.4%) 7 (2.4%)	 5 (2.1%) 3 (1.3%) 2 (0.8%) 3 (1.3%)

	Placebo	Eplerenone		
		25 mg/day	50 mg/day	100 mg/day
Subjects	244	97	294	239
Metabolic				
Creatine Phosphokinases Increased	2 (0.8%)	0	4 (1.4%)	4 (1.7%)
Hypercholesterolemia	0	0	5 (1.7%)	3 (1.3%)
Hypertriglyceridemia	3 (1.2%)	0	4 (1.4%)	6 (2.5%)
Hyperuricemia	2 (0.8%)	0	4 (1.4%)	4 (1.7%)
Musculoskeletal System Disorders				
Arthralgia	1 (0.4%)	0	4 (1.4%)	3 (1.3%)
Respiratory System Disorders				
Bronchitis	3 (1.2%)	1 (1.0%)	2 (0.7%)	4 (1.7%)
Coughing	2 (0.8%)	0	3 (1.0%)	3 (1.3%)
Sinusitis	5 (2.0%)	3 (3.1%)	6 (2.0%)	8 (3.3%)
Upper respiratory Tract Infection	10 (4.1%)	5 (5.2%)	17 (5.8%)	13 (5.4%)
Urinary System Disorders				
Albuminuria	2 (0.8%)	0	3 (1.0%)	3 (1.3%)

Gynecomastia and abnormal vaginal bleeding were reported with eplerenone (around 1%) but not with placebo. The rates increased with increasing duration of therapy.

Clinical Chemistry Findings

EMPHASIS-HF study: NYHA Class II chronic heart failure

A summary of the incidence of hyperkalemia and hypokalemia is provided in **Table 5**.

Table 5. Rates of Hyperkalemia and Hypokalemia - Treated Patients in EMPHASIS-HF Study

Serum potassium mmol/L	Eplerenone N=1344	Placebo N=1349	P-value
>6.0	2.7%	2.1%	0.3141
>5.5	12.9%	8.2%	<0.0001
<4.0	42.0%	51.7%	<0.0001
<3.5	9.0%	12.3%	0.0060
>5.5 at least 2 consecutive measurements	1.6%	0.9%	0.1182

The higher risk of hyperkalemia in patients with renal impairment and, low estimated glomerular filtration rate (eGFR) and history of diabetes mellitus (EMPHASIS-HF study) are shown in **Table 6** and **Table 7** respectively.

Table 6. Rates of Hyperkalemia (>5.5 mmol/L) in EMPHASIS-HF by Baseline Creatinine Clearance*

Baseline Creatinine Clearance	Eplerenone	Placebo
30 mL/min	21.4%	5.6%
31–50 mL/min	15.8%	11.8%
51–70 mL/min	13.8%	7.9%
>70 mL/min	10.0%	6.7%

* Estimated using the Cockroft-Gault formula.

Table 7. Rates of Hyperkalemia (>5.5 mmol/L) in EMPHASIS-HF by baseline eGFR 30-50* and History of Diabetes

	Eplerenone	Placebo
eGFR 30-<50, No Diabetes	15.4%	7.6%
eGFR ≥50, Diabetes	13.6%	8.6%
eGFR 30-<50, Diabetes	21.8%	17.6%
eGFR ≥50, No Diabetes	10.7%	7.0%

EPHESUS study: Post-myocardial infarction heart failure

A summary of the incidence of hyperkalemia and hypokalemia is provided in **Table 8**.

Table 8. Rates of Hyperkalemia and Hypokalemia - Treated Patients in EPHESUS Study

Serum potassium mmol/L	Eplerenone N=1344	Placebo N=1349	P-value
>6.0	4.2%	2.7%	0.001
>5.5	15.6%	11.2%	<0.001
<4.0	42.6%	52.2%	<0.001
<3.5	8.4%	13.1%	<0.001
>5.5 at least 2 consecutive measurements	3.0%	1.7%	<0.001

The higher risk of hyperkalemia in patients with renal impairment and, proteinuria and history of diabetes mellitus (EPHESUS study) are shown in **Table 9** and **Table 10** respectively.

Table 9. Rates of Hyperkalemia (>5.5 mmol/L) in EPHESUS by Baseline Creatinine Clearance*

Baseline Creatinine Clearance	Eplerenone	Placebo
≤30 mL/min	31.5%	22.6%
31–50 mL/min	24.1%	12.7%
51–70 mL/min	16.9%	13.1%
>70 mL/min	10.8%	8.7%

* Estimated using the Cockroft-Gault formula.

Table 10. Rates of Hyperkalemia (>5.5 mmol/L) in EPHESUS by Proteinuria and History of Diabetes*

	Eplerenone	Placebo
Proteinuria, No Diabetes	16.1%	10.8%
No Proteinuria, Diabetes	18.0%	12.9%
Proteinuria and Diabetes	26.0%	15.9%
No Proteinuria, No Diabetes	12.8%	10.3%

*Diabetes assessed as positive medical history at baseline; proteinuria assessed by positive dipstick urinalysis at baseline.

Creatinine: Increases of more than 44 µmol/L were reported in 6.5% of patients administered eplerenone and in 4.9% of placebo-treated patients.

Blood Urea Nitrogen: In EPHESUS, a mean increase of 0.17 mmol/L in blood urea nitrogen (BUN) was reported in patients treated with eplerenone and a mean 0.31 mmol/L decrease for placebo-treated patients. BUN increased in 1.6% and 1.0% of subjects, respectively. The incidence of patients with a value of 1.3xULN for BUN is 36.0% for the eplerenone group compared to 30.5% for placebo.

Abnormal Hematologic and Clinical Chemistry Findings in Hypertension Trials

Potassium: In the combined controlled trials, hyperkalemia rate increased with decreasing renal function, and increased with the co-administration with other antihypertensive drugs as shown in Table 11 below. It is noted that in the trial some patients were treated with higher than the maximal recommended dose of 50 mg twice daily.

Table 11. Maximal Serum Potassium >5.5 mmol/L and >5.9 mmol/L by Baseline Creatinine Clearance in the Combined Controlled Hypertension Trials*

Baseline Creatinine Clearance	Maximum Potassium (mmol/L)	Placebo % (patient #)	Eplerenone monotherapy % (patient #)	Co-Administration therapy % (patient #)
<50 mL/min	>5.5	0 (0/6)	18.2% (6/33)	33.3 (3/9)
	>5.9	0 (0/6)	6.1 % (2/33)	11.1 (1/24)
50 – 70 mL/min	>5.5	0 (0/35)	7.5 (12/160)	17.2 (15/87)
	>5.9	0 (0/35)	2.5% (4/160)	4.6 (4/87)
>70 – 100 mL/min	>5.5	2.5 (3/121)	5.0 (31/624)	12.1 (33/272)
	>5.9	1.7 (2/121)	1.1 (7/624)	2.6 (7/272)
>100 mL/min	>5.5	0.8 (2/252)	2.7 (27/1014)	3.9 (22/563)
	>5.9	0.4 (1/252)	0.7 (7/1014)	1.2 (7/563)

*It is noted that in these trials some patients were treated with higher than maximal recommended dose of 50 mg twice daily.

Sodium: Hyponatremia (<135 mmol/L) was reported for 0% of placebo-treated patients, 0% in 25 mg daily eplerenone group, 0.7% in 50 mg daily eplerenone group and 2.1% in 100 mg daily eplerenone group.

Triglycerides: Increases in triglycerides (above 2.83 mmol/L) were reported for 6.5% in placebo group, 9.2% in 25 mg eplerenone group, 6.0% in 50 mg daily eplerenone group and 7.8% in 100 mg daily eplerenone group.

Cholesterol: Increases in serum cholesterol values greater than 5.17 mmol/L were reported for 0% in placebo group, 0% in 25 mg daily eplerenone group, 1.7% in 50 mg daily eplerenone group and 1.3% in 100 mg daily eplerenone group.

Less Common Clinical Trial Adverse Events

EMPHASIS-HF study: NYHA Class II chronic heart failure

Table 12. Incidence of Adverse Events <2%* of Subjects in the eplerenone arm and more frequent than placebo, in the EMPHASIS-HF Study

Blood and lymphatic system disorders	**Uncommon**: Thrombocytopenia
Cardiac Disorders	**Common**: Bradycardia **Uncommon**: Acute myocardial infarction, Cardiac asthma, Cardiogenic shock, Cardiovascular disorder, Congestive cardiomyopathy, Coronary artery disease, Extrasystoles, Mitral valve incompetence, Sinus tachycardia, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular fibrillation
Eye disorders	**Uncommon**: Conjunctival hemorrhage, Glaucoma, Vision blurred
Gastrointestinal disorders	**Common**: Dyspepsia, Gastritis, **Uncommon**: Abdominal pain upper, Anal fissure, Ascites, Duodenitis, Hemorrhoids, Inguinal hernia, Toothache
General disorders and administration site conditions	**Uncommon**: Influenza like illness, Malaise, Pain
Immune system disorders	**Uncommon**: Hypersensitivity
Infections and infestations	**Common**: Gastroenteritis, Influenza **Uncommon**: Cellulitis, Gangrene, Gastroenteritis viral, Gastrointestinal infection, Herpes zoster, Implant site infection, Localised infection, Lung infection, Pharyngitis, Pyelonephritis, Sinusitis, Tooth abscess, Tooth infection, Viral infection
Injury, poisoning and procedural complications	**Common**: Fall **Uncommon**: Laceration, Ligament sprain, Radius fracture, Road traffic accident, Upper limb fracture
Investigations	**Common**: Blood creatinine increased, Blood urea increased **Uncommon**: Alanine aminotransferase increase, Blood glucose increased, Blood potassium increased, Blood uric acid increased, Epidermal growth factor receptor, Glomerular filtration rate decrease, Hemoglobin decreased, Hepatic enzyme increased, International normalised ratio increase, Liver function test abnormal, Weight decreased, Weight increased
Metabolism and nutrition disorders	**Common**: Dehydration **Uncommon**: Decreased appetite, Dyslipidemia, Hyponatremia, Hypovolemia, Iron deficiency
Musculoskeletal and connective tissue disorders	**Common**: Arthralgia, Muscle spasms, Osteoarthritis **Uncommon**: Bursitis, Muscular weakness, Musculoskeletal chest pain, Musculoskeletal pain, Osteitis, Osteochondrosis, Osteoporosis
Neoplasms benign, malignant and unspecified	**Uncommon**: Bronchial carcinoma, Colon neoplasm, Lung neoplasm
Nervous system disorders	**Uncommon:** Carotid artery stenosis, Carpal tunnel syndrome, Dementia, Diabetic neuropathy, Dizziness postural, Dysarthria, Hypoesthesia, Neuralgia, Neuropathy peripheral, Paresthesia, Polyneuropathy
Psychiatric disorders	**Uncommon:** Anxiety, Depressed mood
Renal and urinary disorders	**Uncommon:** Nocturia, Pollakiuria, Renal failure chronic, Urinary retention
Respiratory, thoracic and mediastinal disorders	**Uncommon:** Acute pulmonary oedema, Hemoptysis, Lung disorder, Nasal congestion, Pneumothorax, Productive cough
Skin and subcutaneous tissue disorders	**Uncommon:** Dermatitis allergic, Psoriasis, Rash, Skin lesion

Surgical and medical procedures	**Uncommon:** Cardiac pacemaker replacement, Prophylaxis
Vascular disorders	**Uncommon:** Extremity necrosis, Intermittent claudication, Peripheral coldness, Phlebitis

*[common: >1% - < 2%; uncommon >0.1%≤1%)]

EPHESUS study: Post-myocardial infarction heart failure

Table 13. Incidence of Adverse Events <2%* of Subjects in the eplerenone arm and more frequent than placebo, in the EPHESUS Study

Application Site Disorders	**Uncommon**: Injection site reaction
Autonomic Nervous System Disorders	**Uncommon**: Hypotension Postural, Pre-syncope
Body as a Whole - General Disorders	**Common**: Influenza-like symptoms, Vertigo **Uncommon**: Chills, Cyst NOS, Edema, Edema generalized, Face edema, Hot flushes, Laboratory test abnormal, Malaise, Pain, Post-operative incision pain, Respite care, Sternal wound infection
Cardiovascular Disorders, General	**Uncommon**: Circulatory failure, Intra-cardiac thrombus
Central and Peripheral Nervous System Disorders	**Common**: Cramps legs **Uncommon**: Aphasia, Ataxia, Dementia, Dysphonia, Encephalopathy, Hemiparesis, Hypotonia, Paresthesia, Tremor
Disorders, Female	**Uncommon**: Breast neoplasm female, Breast neoplasm malignant female, Leukorrhea, Mastitis acute female, Menstrual disorder, Uterine disorder NOS, Vaginitis, Vaginitis atrophic,
Disorders, Male	**Uncommon**: Benign prostatic hyperplasia, Impotence
Endocrine Disorders	**Uncommon**: Hyperthyroidism, Hypothyroidism
Gastro-intestinal System Disorders	**Common**: Gastritis **Uncommon**: Abdominal distension, Appendicitis, Duodenal ulcer, Duodenitis, Dysphagia, Flatulence, Gastric ulcer, Gastroenteritis, Gastroesophageal reflux, Hematemesis, Hemorrhage rectum, Hemorrhoids, Hernia, Hiatal hernia, Pancreatitis, Peptic ulcer
Hearing and Vestibular Disorders	**Uncommon**: Earache, Tinnitus
Heart Rate and Rhythm Disorders	**Common**: Arrhythmia atrial, Fibrillation ventricular, Palpitation **Uncommon**: AV block, Tachycardia, Tachycardia supraventricular
Liver and Biliary System Disorders	**Uncommon**: Biliary pain, Cholecystitis, Cholelithiasis, Jaundice, Liver fatty
Metabolic and Nutritional Disorders	**Uncommon**: Acidosis, Dehydration, Hypertriglyceridemia, Hypoproteinemia, Ketosis, Weight decrease
Musculo-Skeletal System Disorders	**Common**: Fracture accidental **Uncommon**: Arthrosis, Osteoporosis, Tendonitis,
Myo Endo Pericardial & Valve Disorders	**Common**: Myocardial ischemia **Uncommon**: Cardiomyopathy, Pericardial effusion,
Neoplasm	**Uncommon**: GI neoplasm malignant, Neoplasm, Pulmonary carcinoma
Platelet, Bleeding & Clotting Disorders	**Uncommon**: Ecchymosis, Prothrombin decreased, Thrombosis arterial leg
Psychiatric Disorders	**Uncommon**: Apathy, Neurosis, Thinking abnormal
Resistance Mechanism Disorders	**Uncommon**: Herpes Zoster, Infection, Infection viral, Moniliasis, Moniliasis genital, Otitis media, Sepsis
Respiratory System Disorders	**Uncommon**: Abnormal breath sounds, Atelectasis, Hyperventilation, Laryngitis, Pharyngitis, Respiratory arrest, Respiratory disorder, Respiratory insufficiency, Rhinitis, Sinusitis, Sputum increased
Skin and Appendages Disorders	**Common**: Pruritus **Uncommon**: Alopecia, Angioedema, Dermatitis, Inflammation, Rash Maculo-papular, Skin dry, Sweating increased, Urticaria

Special Senses Other, Disorders	**Uncommon**: Taste perversion
Urinary System Disorders	**Common**: Albuminuria, Bun increased **Uncommon**: Bladder carcinoma, Hydronephrosis, Micturition frequency, Nocturia, Polyuria, Pyelonephritis, Renal calculus, Renal cyst, Urinary incontinence, Urinary retention
Vascular (Extracardiac) Disorders	**Uncommon**: Cerebral hemorrhage, Claudication intermittent, Gangrene, Peripheral ischemia, Peripheral vascular disease, Phlebitis, Thrombophlebitis, Vein varicose
Vision Disorders	**Uncommon**: Diplopia, Retinal disorder
White Cell and RES Disorders	**Uncommon**: Eosinophilia, Leukocytosis, Leukopenia, Lymphadenopathy, Lymphocytosis

*[common: >1% - < 2%; uncommon >0.1%≤1%)]

Hypertension Trials: the pooled placebo-controlled, fixed-dose eplerenone hypertension studies data

Table 14. Incidence of Adverse Events <1% of Subjects in the eplerenone arms and more frequent than placebo, in the placebo-controlled, fixed-dose Study

Application Site Disorders	Cellulitis
Autonomic Nervous System	Syncope, Glaucoma, Mouth Dry
Body as A Whole – General Disordoers	Allergy, Chills, Laboratory test abnormal, Pain
Cardiovascular Disorders	Angina pectoris, ECG abnormal, Myocardial infarction, Arrhythmia (atrial and ventricular), Fibrillation atrial
Central and Peripheral Nervous System Disorders	Cramps legs, Migraine, Neuralgia, Paresthesia, Scotoma, Vertigo
Collagen Disorders	Arthritis Rheumatoid
Female Patients Disorders	Menstrual disorder,
Male Patients Disorders	Libido decreased
Endocrine Disorders	Sialoadenitis
Gastro-Intestinal System Disorders	Diverticulitis, Esophagitis, Gastroesophageal reflux, H Pylori, Hemorrhoids, Oral pain, Stomatitis, Vomiting
Hearing and Vestibular Disorders	Labyrinthine disorder, Tinnitus
Metabolic and Nutritional Disorders	Gout, Hypercalcemia, Hyperchloremia
Musculoskeletal System Disorders	Arthritis, Myalgia
Platelet, Bleeding & Clotting Disorders	Prothrombin decreased, Thrombocytopenia
Psychiatric Disorders	Agitation, Confusion, Depression, Anxiety
Red Blood Cell Disorders	Anemia, Hyperhemoglobinemia
Resistance Mechanism Disorders	Herpes zoster, Infection bacterial, Moniliasis genital, Otitis Media, Sepsis
Respiratory System Disorders	Bronchospasm, Laryngitis, Rhinitis, Sputum Increased

Skin and appendages Disorders	Eczema, Nail disorder, Rash macolo-papular
Urinary System Disorders	BUN increased, Cystitis, Hematuria, Oligura, Renal function abnormal, Renal pain, Urine abnormal, Micturition Frequency
Vision Disorders	Blurred vision, Vision abnormal
White Cell and RES Disorders	Eosinophilia, Granulocytosis, Leukopenia, Monocytosis

DRUG INTERACTIONS

Overview

Inhibitors of CYP3A4
MINT-EPLERENONE (eplerenone) metabolism is predominantly mediated via CYP3A4 and therefore, MINT-EPLERENONE should not be used with drugs described as strong inhibitors of CYP3A4 in their labeling (see CONTRAINDICATIONS, Drug-Drug Interactions – Table 15, and DOSAGE AND ADMINISTRATION).

Caution should be used in patients treated with mild to moderate CYP3A4 inhibitors; dosing should not exceed 25 mg QD in patients with an eGFR ≥ 50 mL/min/1.73m^2. For patients with moderate renal impairment (eGFR 30-49 mL/min/1.73 m^2), MINT-EPLERENONE is not recommended because a lower dose than 25 mg once daily has not been studied.

Inducers of CYP3A4
St. John's Wort was found to decrease exposure and to increase clearance of eplerenone significantly indicating that concomitant use of strong inducers of CYP3A4 such as phenobarbital, phenytoin, rifampicin, carbamazepine should be avoided.

ACE Inhibitors and Angiotensin II Receptor Antagonists
In EPHESUS and EMPHASIS-HF, 3020 (91%) and 1282 (94%) patients, respectively, receiving eplerenone 25 to 50 mg, also received ACE inhibitors or angiotensin II receptor antagonists (ACEI/ARB). Rates of patients with maximum potassium levels >5.5 mmol/L were similar regardless of the use of ACEI/ARB. However, as ACEI/ARB can also increase serum potassium levels in some patients, concomitant use with eplerenone dictates that greater caution should be exercised.

Lithium
A drug interaction study of eplerenone with lithium has not been conducted. However, lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors and concomitant administration of eplerenone may worsen lithium toxicity. Serum lithium levels should be monitored frequently if eplerenone is administered concomitantly with lithium, as excretion may be altered as a result of modifications in sodium balance induced by the aldosterone antagonist. Lithium has also been reported to increase plasma renin activity and aldosterone levels.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

A drug interaction study of eplerenone with an NSAID has not been conducted. The administration of potassium-sparing antihypertensive drugs with NSAIDs has been shown to reduce the antihypertensive effect in some patients and result in severe hyperkalemia in patients with impaired renal function. Therefore, when eplerenone and NSAIDs including COX-2 Inhibitors, are used concomitantly, blood pressure, renal function and serum potassium should be closely monitored.

Herbal Preparations and Salt Substitutes
The full consequence of using eplerenone in patients taking herbal preparations and/or salt substitutes has not been established, and caution should be exercised. Theoretically, patients who are taking herbal preparations that affect blood pressure or contain high levels of potassium may be at risk of hypotension/hypertension or hyperkalemia (see WARNINGS and PRECAUTIONS). Clinicians should consider discontinuing the herbal preparation or salt substitute or closely monitoring patients using such a combination. Such preparations may include (but not limited to): dandelion, potassium iodine, laminaria, morinda, oleander, phosphate salts and potassium preparations, cat's claw, cod liver oil, and licorice.

Drug-Drug Interactions

Drug-drug interaction studies were conducted with a 100 mg dose of eplerenone and the outcomes are summarized in **Table 15**.

Table 15. Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Digoxin	CT	no clinically significant interactions	Systemic Exposure (AUC) to digoxin increases by 16% (90% CI: 4-30%) when co-administered with eplerenone. Caution is warranted when digoxin is dosed near the upper limit of the therapeutic range.
Warfarin	CT	no clinically significant interactions	
CYP3A4 substrates (e.g. midazolam, cisapride)	T and CT	no clinically significant interactions	
Potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin, nefazodone)	T and CT	significant increases in eplerenone AUC	Concomitant use is contraindicated (see CONTRAINDICATIONS)

Proper name	Ref	Effect	Clinical comment
Mild to Moderate CYP3A4 inhibitors (erythromycin, saquinavir, amiodarone, diltiazem, verapamil, fluconazole)	T and CT	significant increases in eplerenone AUC	Eplerenone dosing should not exceed 25 mg daily when mild to moderate inhibitors of CYP3A4 are co-administered (see DOSAGE AND ADMINISTRATION). For patients with moderate renal impairment (eGFR 30-49mL/min/1.73 m^2) eplerenone is not recommended. For hypertension, reduce the dose to 25 mg once daily when used with mild to moderate CYP3A4 inhibitors (e.g., verapamil, erythromycin, saquinavir, fluconazole).
Potent CYP3A4 Inducers (e.g. carbamazepine, phenytoin, Phenobarbital, St John's Wort, rifampicin)	T and CT	decreases eplerenone AUC	Due to the risk of decreased eplerenone efficacy, concomitant use of strong CYP3A4 inducers with eplerenone is not recommended because a lower dose than 25 mg once daily has not been studied.
Aluminum and magnesium- containing antacids	CT	No significant changes in eplerenone pharmacokinetics	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

MINT-EPLERENONE may be administered with or without food.

DOSAGE AND ADMINISTRATION

Glomerular filtration rate should be estimated (eGFR) and serum potassium measured before initiating MINT-EPLERENONE (eplerenone) therapy since MINT-EPLERENONE dosing depends on these variables.

MINT-EPLERENONE should not be administered to heart failure patients with initial serum potassium >5.0 mmol/L, serum creatinine >221µmol/L and/or eGFR <30 mL/min/1.73 m^2.

Serum potassium should be measured before initiating MINT-EPLERENONE (eplerenone) therapy, within the first week and at one month after the start of treatment or after a dose adjustment. Serum potassium should be measured periodically thereafter, as clinically warranted. Hyperkalemia can be expected at any time during treatment with MINT-EPLERENONE.

Efforts should be made to decrease the dietary potassium intake. Patients should be asked about their use of potassium containing salt substitutes and dietary supplements. Factors, such as patient characteristics, serum potassium levels and concomitant medications, may indicate that additional monitoring of serum potassium is appropriate (see WARNINGS AND PRECAUTIONS - Hyperkalemia, ADVERSE REACTIONS, and DRUG INTERACTIONS). MINT-EPLERENONE may be administered with or without food.

Recommended Dose and Dosage Adjustment

Heart failure

Renal Impairment
Patients with eGFR of ≥50 mL/min/1.73 m^2:

For chronic heart failure NYHA Class II and post-myocardial infarction heart failure patients with serum potassium ≤ 5 mmol/L, treatment should be initiated at a dose of 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks, taking into account the serum potassium level (see Table 16). Following myocardial infarction MINT-EPLERENONE should be initiated 3 – 14 days after MI.

The maximum daily dose in patients with eGFR of ≥50 mL/min/1.73 m^2 is 50 mg daily. In patients using a mild to moderate CYP3A4 inhibitor, the maximum daily dose of MINT-EPLERENONE is 25 mg.

Patients with eGFR of 30-49 mL/min/1.73 m^2:
For chronic heart failure NYHA Class II and post-myocardial infarction heart failure patients with serum potassium ≤ 5 mmol/L, treatment should be initiated at a dose of 25 mg once every other day and titrated to the target dose of 25 mg once daily preferably within 4 weeks, taking into account the serum potassium level (see Table 16). Following myocardial infarction MINT-EPLERENONE should be initiated 3 – 14 days after MI.

The maximum dose in patients with an eGFR 30-49 mL/min/1.73 m^2 is 25 mg once daily. MINT-EPLERENONE should not be given to patients on a mild to moderate CYP3A4 inhibitor because a lower dose than 25 mg once daily has not been studied.

Patients with eGFR of <30 mL/min/1.73 m^2: MINT-EPLERENONE is contraindicated in patients with severe renal impairment.

Hepatic Impairment
Mild-to-Moderate Hepatic Impairment: No initial dosage adjustment is necessary.
Severe Hepatic Impairment (see CONTRAINDICATIONS and WARNINGS and PRECAUTIONS).

Dose adjustment based on serum potassium levels for heart failure patients

Patients who develop hyperkalemia (>5.5 mmol/L) may still benefit from MINT-EPLERENONE with proper dose adjustment. The dose should be adjusted based on the serum potassium

level and the dose adjustment table shown in **Table 16**.

Table 16 Dose Adjustment recommendations after initiation

Serum Potassium (mmol/L)	Action	Dose Adjustment
< 5.0	Increase	If 25 mg QOD* to 25 mg QD** If 25 mg QD to 50 mg QD; except (no increase) if: - concurrent mild-moderate CYP3A4 inhibitor or - patients with an eGFR 30-49 ml/min/1.73m^2
5.0-5.4	Maintain	No adjustment
5.5-5.9	Decrease	If 50 mg QD to 25 mg QD If 25 mg QD to 25 mg QOD If 25 mg QOD to withhold; restart ONLY if K^+ falls <5.0
≥ 6.0	Withhold	Restart at a lower dose ONLY when K^+ falls <5.0

*QOD: every other day; **QD: every day

Following withholding MINT-EPLERENONE due to serum potassium ≥6.0 mmol/L and the return of potassium levels within acceptable limits, MINT-EPLERENONE can be restarted at a *test* dose of 25 mg every other day. There are no data to demonstrate that 25 mg every other day is effective and such dosing should be considered to be only a temporary situation. After a test period of one week on 25 mg every other day, serum potassium levels should be measured. If potassium levels return within acceptable limits, the dose can be increased to 25 mg every day and serum potassium should be measured after one week. It could then be determined if MINT-EPLERENONE therapy should be continued or stopped.

Hypertension

MINT-EPLERENONE should not be administered to hypertensive patients with initial serum potassium >5.0 mmol/L, serum creatinine >132 µmol/L in males or >115 µmol/L in females, and/or eGFR<50 mL/min/1.73 m^2.

In patients with hypertension who have reduced eGFR, serum potassium concentrations should be closely monitored when treated with MINT-EPLERENONE, especially when co-administrated with other antihypertensive drugs).

For hypertension, the recommended starting dose of MINT-EPLERENONE is 50 mg administered once daily. The full therapeutic effect of MINT-EPLERENONE is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50 mg once daily the dosage of MINT-EPLERENONE should be increased to 50 mg twice daily. Higher dosages of MINT-EPLERENONE are not recommended because they have no greater effect on blood pressure and are associated with an increased risk of adverse reactions, including hyperkalemia. (See CLINICAL TRIALS)

Specific Populations

Patients with hypertension: for patients with hypertension receiving mild to moderate CYP3A4 inhibitors (e.g., erythromycin, saquinavir, verapamil, and fluconazole), the dose of

MINT-EPLERENONE should be reduced to 25 mg once daily. (See DRUG INTERACTIONS).

OVERDOSAGE

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

In the hypertension clinical trials, increased incidence of hyperkalemia, hyponatremia, hyperglycemia, hypertriglyceridemia, increased GGT, and increased creatinine have been observed with the higher than maximal recommended doses (over 100 mg daily).

No cases of adverse events associated with overdose of eplerenone in humans have been reported. Lethality was not observed in mice, rats, or dogs after single oral doses that provided C_{max} exposures at least 25 times higher than in humans receiving eplerenone 100 mg/day. Dogs showed emesis, salivation, and tremors at a C_{max} 41 times the human therapeutic C_{max}, progressing to sedation and convulsions at higher exposures.

The most likely manifestation of human overdosage would be anticipated to be hypotension and/or hyperkalemia. Eplerenone cannot be removed by hemodialysis. Eplerenone has been shown to bind extensively to charcoal. If symptomatic hypotension should occur, supportive treatment should be instituted. If hyperkalemia develops, standard treatment should be initiated.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Eplerenone binds to the mineralocorticoid receptor and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone-system (RAAS). Aldosterone synthesis, which occurs primarily in the adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators, such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues, and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms through both genomic and non-genomic effects.

Pharmacodynamics

Eplerenone has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effects of eplerenone.

Eplerenone selectively binds to recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

In dose-ranging studies of chronic heart failure (NYHA classification II-IV), the addition of eplerenone to standard therapy resulted in expected dose-dependent increases in aldosterone. Similarly, in a cardiorenal substudy of EPHESUS, therapy with eplerenone led to a significant increase in aldosterone. These results are consistent with blockade of the mineralocorticoid receptor in these populations.

No consistent effects of eplerenone on heart rate, QRS duration, or PR or QT interval were observed in 147 normal subjects evaluated for electrocardiographic changes during pharmacokinetic studies.

Pharmacokinetics

General: Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism, with an elimination half-life of 3 to 6 hours. Steady state is reached within 2 days. Absorption is not affected by food. Inhibitors of CYP3A4 increase blood levels of eplerenone.

Absorption and Distribution: Mean peak plasma concentrations of eplerenone are reached approximately 1.5 to 2 hours following oral administration. The absolute bioavailability of eplerenone is 69% following administration of a 100 mg oral tablet. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 25 to 100 mg and less than proportional at doses above 100 mg.

The plasma protein binding of eplerenone is about 50% and it is primarily bound to alpha L-acid glycoproteins. The apparent volume of distribution at steady state ranged from 42 to 90 L. Eplerenone does not preferentially bind to red blood cells.

Metabolism and Excretion: Eplerenone metabolism is primarily mediated via CYP3A4. No active metabolites of eplerenone have been identified in human plasma.

Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted in the feces and approximately 67% was excreted in the urine. The elimination half-life of eplerenone is approximately 3 to 6 hours. The apparent plasma clearance is approximately 10 L/hr.

Special Populations and Conditions

***Age, Gender, and Race*:** The pharmacokinetics of eplerenone at a dose of 100 mg once daily has been investigated in the elderly (≥65 years), in males and females, and in blacks. The pharmacokinetics of eplerenone did not differ significantly between males and females. At steady state, elderly subjects had increases in C_{max} (22%) and AUC (45%) compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19% lower and AUC was 26% lower in blacks (see WARNINGS AND PRECAUTIONS, Geriatric Use and DOSAGE AND ADMINISTRATION).

***Renal Insufficiency*:** The pharmacokinetics of eplerenone was evaluated in patients with varying degrees of renal insufficiency and in patients undergoing hemodialysis. Compared with

control subjects, steady-state AUC and C_{max} were increased by 38% and 24%, respectively, in patients with severe renal impairment and were decreased by 26% and 3%, respectively, in patients undergoing hemodialysis. No correlation was observed between plasma clearance of eplerenone and creatinine clearance. Eplerenone is not removed by hemodialysis (see WARNINGS AND PRECAUTIONS, Hyperkalemia).

***Hepatic Insufficiency*:** The pharmacokinetics of eplerenone 400 mg has been investigated in patients with moderate (Child-Pugh Class B) hepatic impairment and compared with normal subjects. Steady-state C_{max} and AUC of eplerenone were increased by 3.6% and 42%, respectively (see DOSAGE AND ADMINISTRATION).

***Heart Failure*:** The pharmacokinetics of eplerenone 50 mg was evaluated in 8 patients with heart failure (NYHA classification II-IV) and 8 matched (gender, age, weight) healthy controls. Compared with the controls, steady state AUC and C_{max} in patients with stable heart failure were 38% and 30% higher, respectively.

Drug-Drug Interactions
(see DRUG INTERACTIONS)

Drug-drug interaction studies were conducted with a 100 mg dose of eplerenone.

Eplerenone is metabolized primarily by CYP3A4. A potent inhibitor of CYP3A4 (ketoconazole) caused increased exposure of 5.4 fold; while less potent CYP3A4 inhibitors (erythromycin, saquinavir, verapamil, and fluconazole) resulted in increases ranging from 2.0-2.9 fold. Grapefruit juice caused only a small increase (about 25%) in exposure (see DRUG INTERACTIONS).

Eplerenone is not an inhibitor of CYP1A2, CYP3A4, CYP2C19, CYP2C9, or CYP2D6. Eplerenone did not inhibit the metabolism of amiodarone, amlodipine, astemizole, chlorzoxazone, cisapride, dexamethasone, dextromethorphan, diclofenac, 17α-ethinyl estradiol, fluoxetine, losartan, lovastatin, mephobarbital, methylphenidate, methylprednisolone, metoprolol, midazolam, nifedipine, phenacetin, phenytoin, simvastatin, tolbutamide, triazolam, verapamil, and warfarin in vitro. Eplerenone is not a substrate or an inhibitor of P-Glycoprotein at clinically relevant doses.

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

No significant changes in eplerenone pharmacokinetics were observed when eplerenone was administered with aluminum and magnesium-containing antacids.

STORAGE AND STABILITY

Store at controlled room temperature (15–30ºC).

SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

MINT-EPLERENONE (eplerenone) tablets are formulated for oral administration and are available in tablet doses of 25 mg and 50 mg.

Composition

MINT-EPLERENONE tablets contain either 25 mg or 50 mg of eplerenone as the active ingredient.

The non-medicinal ingredients are as follows: croscarmellose sodium, D&C Yellow #10 Aluminium Lake, FD&C Yellow #6 Aluminimum lake, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, lactose monohydrate, polyethylene glycol, magnesium stearate, microcrystalline cellulose, polysorbate 80, sodium lauryl sulfate, talc, titanium dioxide.

Packaging

MINT-EPLERENONE tablets, 25 mg, are yellowish red colour diamond shaped biconvex film-coated tablets. They are debossed with “E” on one side and “25” on the other. They are available in bottles of 30 and 90, and blister packs of 100 (cartons of 10 x 10).

MINT-EPLERENONE tablets, 50 mg, are yellowish red colour diamond shaped biconvex film-coated tablets. They are debossed with “E” on one side and “50” on the other. They are available in bottles of 30 and 90, and blister packs of 100 (cartons of 10 x 10).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

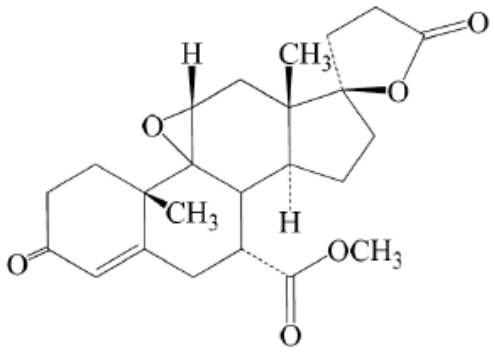
Drug Substance

Common name: Eplerenone

Chemical name: Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, methyl ester, (7α,11α,17α)-

Molecular formula and molecular mass: $C_{24}H_{30}O_6$
414.49 g/mol

Structural formula:



Physicochemical properties: Eplerenone is an odorless, white to off-white crystalline powder. It is very slightly soluble in water, with its solubility essentially pH independent. The octanol/water partition coefficient of eplerenone is approximately 7.1 at pH 7.0.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, blinded, two-treatment, two-period, two-sequence, single dose, bioequivalence study between 1 x MINT-EPLERENONE (eplerenone) 50 mg tablets (Mint Pharmaceuticals Inc.) and 1 x INSPRA® (eplerenone) 50 mg tablets (Pfizer Canada Inc.) was conducted in healthy Asian male subjects (from 22 to 44 years of age) under fasting conditions (n = 30). The results from 26 subjects are presented below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

EPLERENONE (1 x 50 mg) From measured data Geometric Mean Arithmetic Mean (%CV)				
Pharmacokinetic Parameter	TEST*	REFERENCE†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (hr.ng/mL)	6867.4 7210.9 (31.6%)	6861.1 7151.4 (28.1%)	102.7	96.0 - 109.8
AUC_I (hr.ng/mL)	6999.4 7352.7 (31.8%)	7000.5 7300.0 (28.3%)	102.6	96.0 - 109.6
C_{max} (ng/mL)	1142.7 1163.2 (19.8%)	1097.5 1111.2 (16.3%)	105.1	98.6 - 112.0
T_{max}§ (hr)	1.0 (0.5 - 3.5)	1.3 (0.3 - 3.0)		
$T_{½}$@ (hr)	4.1 (31.7%)	4.1 (24.6%)		

* MINT-EPLERENONE (eplerenone) 50 mg tablets (Mint Pharmaceuticals Inc.)
† Pr INSPRA® (eplerenone) 50 mg tablets (Pfizer Canada Inc.) were purchased in Canada
§ Expressed as the median (range) only
@ Expressed as the Arithmetic mean (%CV) only

EMPHASIS-HF study: NYHA Class II chronic heart failure

In the EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) the effect of eplerenone when added to standard therapy on clinical outcomes was investigated in patients with systolic heart failure and mild symptoms (NYHA functional class II).

Patients were included if they were at least 55 years old, had a left ventricular ejection fraction (LVEF) ≤30% (or LVEF ≤35% only if QRS duration was >130 msec) and were either hospitalized for cardiovascular (CV) reasons less than 6 months prior to inclusion or had a plasma level of B-type natriuretic peptide (BNP) of at least 250 pg/ml or a plasma level of N- terminal pro-BNP of at least 500 pg/ml in men (750 pg/ml in women). Patients enrolled were still symptomatic, albeit mildly, in spite of recommended standard therapy (Table 18). The main exclusion criteria

were a contraindication to eplerenone, severe heart failure, recent stroke or MI, cardiac surgery, uncontrolled hypertension (diastolic >110 and or systolic >180 mmHg), symptomatic hypotension, need for potassium-sparing diuretics, surgically amenable cause of HF, intra-aortic pump or other assist device, concomitant potent inhibitor or inducer of CPY3A4, hemoglobin <10 g/dL, significant liver disease, alcohol abuse, progressive fatal disease, pregnancy or no acceptable method of contraception, other acute or chronic medical or psychiatric conditions or laboratory abnormalities that could increase the risk associated with participation in the trial or product administration that would interfere with the interpretation of the results.

In patients with eGFR ≥50 ml/min/1.73 m^2, eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily if the serum potassium level was <5.0 mmol/L. Alternatively, if the estimated GFR was 30-49 mL/min/1.73 m^2, eplerenone was started at 25 mg on alternate days for 4 weeks, and then increased to 25 mg once daily only if serum potassium levels remained <5.0 mmol/L.

In total, 2737 patients were randomized (double-blind) to the treatment with eplerenone or placebo. They presented with concurrent medical conditions (at screening) listed in Table 17 and they received the concomitant treatments shown in Table 18. Patients on eplerenone were followed-up for a median duration of 533 days and on placebo for a median duration of 494 days.

Demographic and baseline characteristics were generally well matched with some exceptions when there were only a limited number of patients for a given characteristic. Most were males (77-78%), white (83%), had ischemic heart failure (69%) for a mean duration of 5.35 years, a significant medical condition (97%) the most common being hypertension (45%) and/or prior MI (50%), angina (43%), diabetes mellitus (31%), and had been hospitalized for congestive HF (53%).

TABLE 17 - Significant medical conditions in ≥10% of subjects in eplerenone and placebo treatment groups at screening.

Concomitant Condition	Percent (%) of patients (rounded)	
	Eplerenone N=1364	**Placebo** N= 1373
Angina pectoris	43	44
Hypertenstion	67	66
Diabetes Mellitus	34	29
Chronic obstructive pulmonary disease (COPD)	15	14
Coronary artery bypass grafting	19	19
Precutaneous coronary	22	22
revascularization Implanted	13	13
cardioverter defibrillator Pacemaker	14	15
implanted	30	32
Atrial fibrillation/flutter		

TABLE 18 - Summary of selected prior and concomitant drug treatments

Prior or Concomitant Treatment	Percent (%) of patients	
	Eplerenone N= 1364	Placebo N=1373
Drug treatment before start of study treatment	81	80
ACE inhibitor, alone or combination	21	20
ARB, alone or combination	95	94
ACE or ARB	88	89
Beta-blockers*	87	88
Diuretics	90	90
Antithrombotic agents**		
Drug treatment at randomization visit		
ACE inhibitor, alone or combination	81	80
ARB, alone or combination	25	25
ACE or ARB	96	95
Beta-blockers*	87	87
Diuretics	84	86
Antithrombotic agents**	88	88
Concomitant drug treatments	78	77
ACE inhibitor, alone or combination	19	19
ARB, alone or combination	94	93
ACE or ARB	90	91
Beta-blockers*	88	90
Diuretics	91	91
Antithrombotic agent**		

* Mainly carvedilol, metoprolol and bisoprolol

** Mainly ASA and clopidogrel

The primary endpoint, death from cardiovascular causes or hospitalization for heart failure occurred in 249 patients (18.3%) in the eplerenone group and 356 patients (25.9%) in the placebo group (RR 0.63, 95% CI, 0.54-0.74; p<0.001). The effect of eplerenone on the primary endpoint outcomes was consistent across all pre-specified subgroups (see Table 19).

TABLE 19. Survival analysis for the composite primary endpoint and its components (cardiovascular death or hospitalization for heart failure). The adjusted* values are in plain font and unadjusted values are shown in italic.

EVENT	Number (%) of patients		HR and (95% CI)	p-value	ARR %	RRR %
	Eplerenone N=1364	Placebo N=1373				
CV death/HF hospitalization	249 (18.3)	356 (25.9)	0.63 (0.535, 0.741) *0.66 (0.561, 0.0776)*	<0.0001 *<0.0001*	7.6	30
CV death	147 (10.8)	185 (13.5)	0.76 (0.609, 0.941) *0.77 (0.620, 0.956)*	0.0120 *0.018*	2.7	20
HF hospitalization	164 (12.0)	253 (18.4)	0.58 (0.473, 0.702) *0.61 (0.503, 0.746)*	<0.0001 *<0.0001*	6.4	35

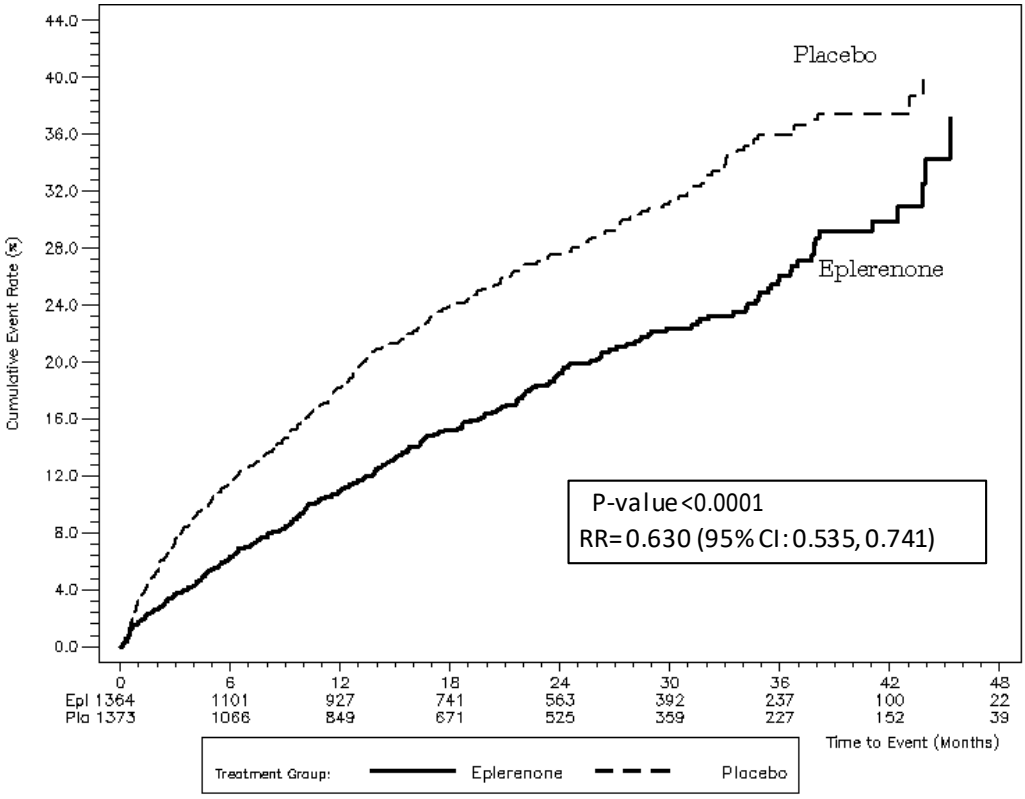
CI = confidence interval; **CV** = cardiovascular; **HF** = heart failure; **HR =** hazard ratio; **ARR =** absolute risk reduction; **RRR** = relative risk reduction.

* Hazard ratio, 95% CI of hazard ratio, and p-value were based on a Cox proportional hazard model including treatment as the major factor, adjusting for age, eGFR, LVEF, BMI, hemoglobin, heart rate, SBP, diabetes, history of hypertension, prior MI, baseline LBBB or QRS>130 msec, and atrial fibrillation as covariates.

During the study, hyperkalemia (serum potassium level > 5.5 mmol/L) was reported in 173 patients (12.9%) in the eplerenone group and 111 patients (8.2%) in the placebo group ($p < 0.001$). Hypokalemia, defined as serum potassium levels < 4.0 mmol/L, was statistically lower with eplerenone when compared to placebo (42.0% for eplerenone compared to 52.7% for placebo, $p<0.0001$). These results are summarized in Table 2, found under the ADVERSE REACTIONS section.

Kaplan-Meier estimates of CV death or hospitalization for heart failure are shown in **Figure 1** and the components of cardiovascular mortality or hospitalization are provided in **Table 20**.

Figure 1. Survival Plot of Time to First Event of Heart Failure Hospitalization or Cardiovascular Death



The secondary endpoint of all cause mortality was met by 171 patients (12.5%) in the eplerenone group and 213 patients (15.5%) in the placebo group (HR 0.76; 95% CI, 0.62-0.93; p = 0.008). Death from CV causes was reported in 147 (10.8%) patients in the eplerenone group and 185 (13.5%) patients in the placebo group (HR 0.76; 95% CI, 0.61-0.94; p = 0.01). Hospitalization for heart failure occurred in 164 (12.0%) in the eplerenone group as compared with 253 (18.4%) patients in the placebo group (HR 0.58; 95% CI, 0.47-0.70; p<0.001). Results from other secondary endpoints are also summarized in **Table 21.**

Table 20. Summary of Causes for Cardiovascular Death and Cardiovascular Hospitalization (Full Analysis Set)

	Eplerenone	Placebo
Total number of subjects	1364	1373
Number (%) of subjects with HF hospitalization or CV death	249 (18.3)	356 (25.9)
Number (%) of subjects with HF hospitalization	164 (12.0)	253 (18.4)
Number (%) of subjects with CV death	147 (10.8)	185 (13.5)
Sudden cardiac death	60 (4.4)	76 (5.5)
Worsening heart failure	45 (3.3)	61 (4.4)
Myocardial infarction	13 (1.0)	8 (0.6)
Arrhythmia	7 (0.5)	7 (0.5)
Stroke	6 (0.4)	7 (0.5)
Emergency CV procedure/operation	0	0
Other CV event	3 (0.2)	1 (0.1)
Unknown[a]	13 (1.0)	25 (1.8)
Number (%) subjects with CV hospitalization	304 (22.3)	399 (29.1)
Heart failure	164 (12.0)	253 (18.4)
Arrhythmia	49 (3.6)	74 (5.4)
Myocardial infarction, unstable angina, other chest pain	68 (5.0)	61 (4.4)
Stroke, TIA	25 (1.8)	32 (2.3)
Syncope/near syncope, hypotension	19 (1.4)	18 (1.3)
Cardiac tamponade, endocarditis, hypertension, valvular heart disease, other CV event, other	25 (1.8)	40 (2.9)
Pulmonary embolism	1 (0.1)	2 (0.1)
Other peripheral arterial problem	13 (1.0)	11 (0.8)
Ruptured aneurysm	1 (0.1)	0

HF = heart failure; CV = cardiovascular; TIA = transient ischemic attack.
a: Death without sufficient data on the cause of the death was adjudicated as death with unknown cause, which is defaulted into the CV death category according to protocol

Table 21. Survival Analysis of the Secondary Endpoints

	Number (%) of Subjects		HR	P-value	95% CI	ARR %	RRR %
	Eplerenone (N=1364)	Placebo (N=1373)					
All-cause mortality or HF hospitalization	270 (19.8)	376 (27.4)	0.647	<0.0001	0.552, 0.757	7.6	30
All-cause mortality	171 (12.5)	213 (15.5)	0.761	0.0081	0.622, 0.932	3.0	19
CV mortality	147 (10.8)	185 (13.5)	0.757	0.0120	0.609, 0.941	2.7	20
All-cause hospitalization	408 (29.9)	491 (35.8)	0.768	<0.0001	0.673, 0.876	5.9	16
HF hospitalization	164 (12.0)	253 (18.4)	0.576	<0.0001	0.473, 0.702	6.4	35
All-cause death or all cause hospitalization	462 (33.9)	569 (41.4)	0.751	<0.0001	0.664, 0.849	7.5	18
CV hospitalization	304 (22.3)	399 (29.1)	0.694	<0.0001	0.598, 0.806	6.8	3523
Hospitalization for hyperkalemia	4 (0.3)	3 (0.2)	1.154	0.8539	0.251, 5.312		

* HR = Hazard Ratio; ARR=Absolute Risk Reduction; RRR= Relative Risk Reduction

In 330 eplerenone and 327 placebo patients ≥ 75 years of age (subgroup analysis), the statistical significance of the composite primary endpoint rates (HR 0.66, p=0.005) was driven by a significant reduction in hospitalization for heart failure (HR 0.55, p=0.0007) as there was no statistically significant reduction in cardiovascular mortality (HR 0.98; p=0.92). The analysis also showed significant reductions (p<0.003) in both CV hospitalization and all cause hospitalization, while it did not show a difference for all-cause mortality, fatal/non-fatal MI or fatal/non-fatal stroke in these elderly patients.

Heart Failure Post-Myocardial Infarction

The eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS) was a multinational, multicentre, double-blind, randomized, placebo-controlled study in patients clinically stable 3-14 days after an acute myocardial infarction (MI) with left ventricular dysfunction (as measured by left ventricular ejection fraction [LVEF] ≤40%) and either diabetes or clinical evidence of heart failure (HF) (pulmonary congestion by exam or chest x-ray or S_3). Patients with HF of valvular or congenital etiology, patients with unstable post- infarct angina, and patients with serum potassium >5.0 mmol/L or serum creatinine >221µmol/L were to be excluded. Patients were allowed to receive standard post-MI drug therapy and to undergo revascularization by angioplasty or coronary artery bypass graft surgery.

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

EPHESUS randomized 6,632 patients at 671 centers in 27 countries. The study population was primarily Caucasian (90%, with 1% black, 1% Asian, 6% Hispanic, 2% other) and male (71%). The mean age was 64 years (range, 22-94 years). The majority of patients had pulmonary congestion (75%) by exam or x-ray and were Killip Class II (64%). The mean ejection fraction was 33%. The average time to enrollment was 7 days post-MI. Medical histories prior to the index MI included hypertension (60%), coronary artery disease (62%), dyslipidemia (48%), angina (41%), type 2 diabetes (30%), previous MI (27%), and HF (15%).

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

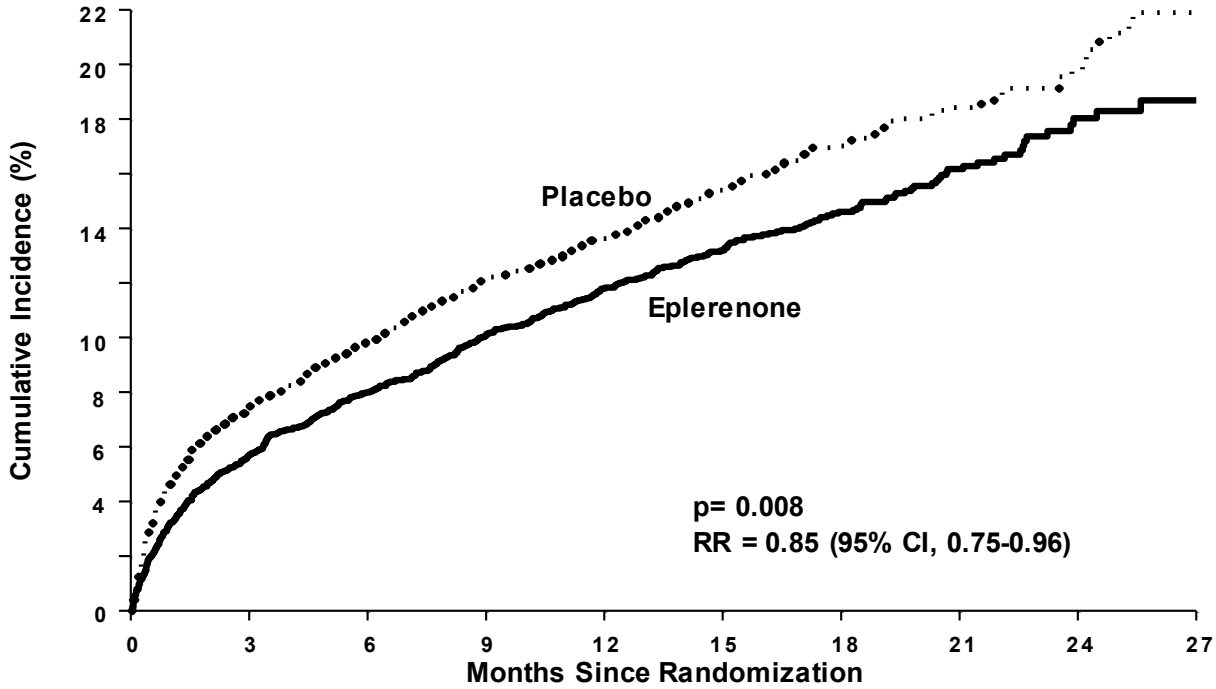
Patients were followed for an average of 16 months (range, 0-33 months). The ascertainment rate for vital status was 99.7%.

The co-primary endpoints for EPHESUS were (1) the time to death from any cause, and (2) the time to first occurrence of either cardiovascular (CV) mortality [defined as sudden cardiac death or death due to progression of heart failure (HF), stroke, or other CV causes] or CV hospitalization (defined as hospitalization for progression of HF, ventricular arrhythmias, acute myocardial infarction, or stroke). To maintain an overall type I error rate of 0.05 (two-sided), the rate of death from any cause was tested at the 0.04 level of significance and the rate of death

from cardiovascular causes or hospitalization for cardiovascular events was tested at the 0.01 level of significance.

For the co-primary endpoint for death from any cause, there were 478 deaths in the eplerenone group (14.4%) and 554 deaths in the placebo group (16.7%). The risk of death with eplerenone was reduced by 15% [hazard ratio equal to 0.85 (95% confidence interval 0.75 to 0.96; p = 0.008 by log rank test)]. Kaplan-Meier estimates of all-cause mortality are shown in **Figure 2** and the components of mortality are provided in **Table 22**.

Figure 2. Kaplan-Meier Estimates of All-Cause Mortality



No. at Risk:

Placebo	3313	3064	2983	2830	2418	1801	1213	709	323	99
Eplerenone	3319	3125	3044	2896	2463	1857	1260	728	336	110

It can be seen in **Table 22** that the effect on total mortality is driven by a decrease in CV mortality. Most CV deaths were attributed to sudden death, acute MI, and HF.

Table 22 - Summary of Events Contributing to All Cause Mortality (Intent-to-Treat Population)

	Eplerenone N=3319	**Placebo** N=3313	p-value	Relative Risk Ratio (RRR)	95% CI for RRR
Deaths - all causes	478 (14.4%)	554 (16.7%)	0.008	0.85	(0.75, 0.96)
CV deaths	407 (12.3%)	483 (14.6%)	0.005	0.83	(0.72, 0.94)
Sudden	162 (4.9%)	201 (6.1%)	0.025	0.79	(0.64, 0.97)
Recurrent AMI	78 (2.4%)	94 (2.8%)	0.187	0.82	(0.61, 1.10)
HF	104 (3.1%)	127 (3.8%)	0.096	0.80	(0.62, 1.04)
Stroke	26 (0.8%)	28 (0.6%)	0.734	0.91	(0.53, 1.55)
Aneurysm	1 (0.0%)	1 (0.0%)	0.998	0.98	(0.06, 15.64)
Pulmonary embolism	4 (0.1%)	4 (0.1%)	0.977	0.98	(0.25, 3.92)
Other CV deaths	32 (1.0%)	28 (0.8%)	0.672	1.12	(0.67, 1.85)
Non-CV deaths	60 (1.8%)	54 (1.6%)	0.644	1.09	(0.75, 1.58)
Sepsis	9 (0.3%)	7 (0.2%)	0.657	1.25	(0.47, 3.36)
Pneumonia	10 (0.3%)	8 (0.2%)	0.675	1.22	(0.48, 3.09)
Cancer	20 (0.6%)	19 (0.6%)	0.918	1.03	(0.55, 1.94)
Other non-CV deaths	21 (0.6%)	20 (0.6%)	0.909	1.04	(0.56, 1.91)
Unwitnessed deaths	0	1 (0.0%)			
Unknown cause	11 (0.3%)	16 (0.5)	0.314	0.68	(0.31, 1.46)

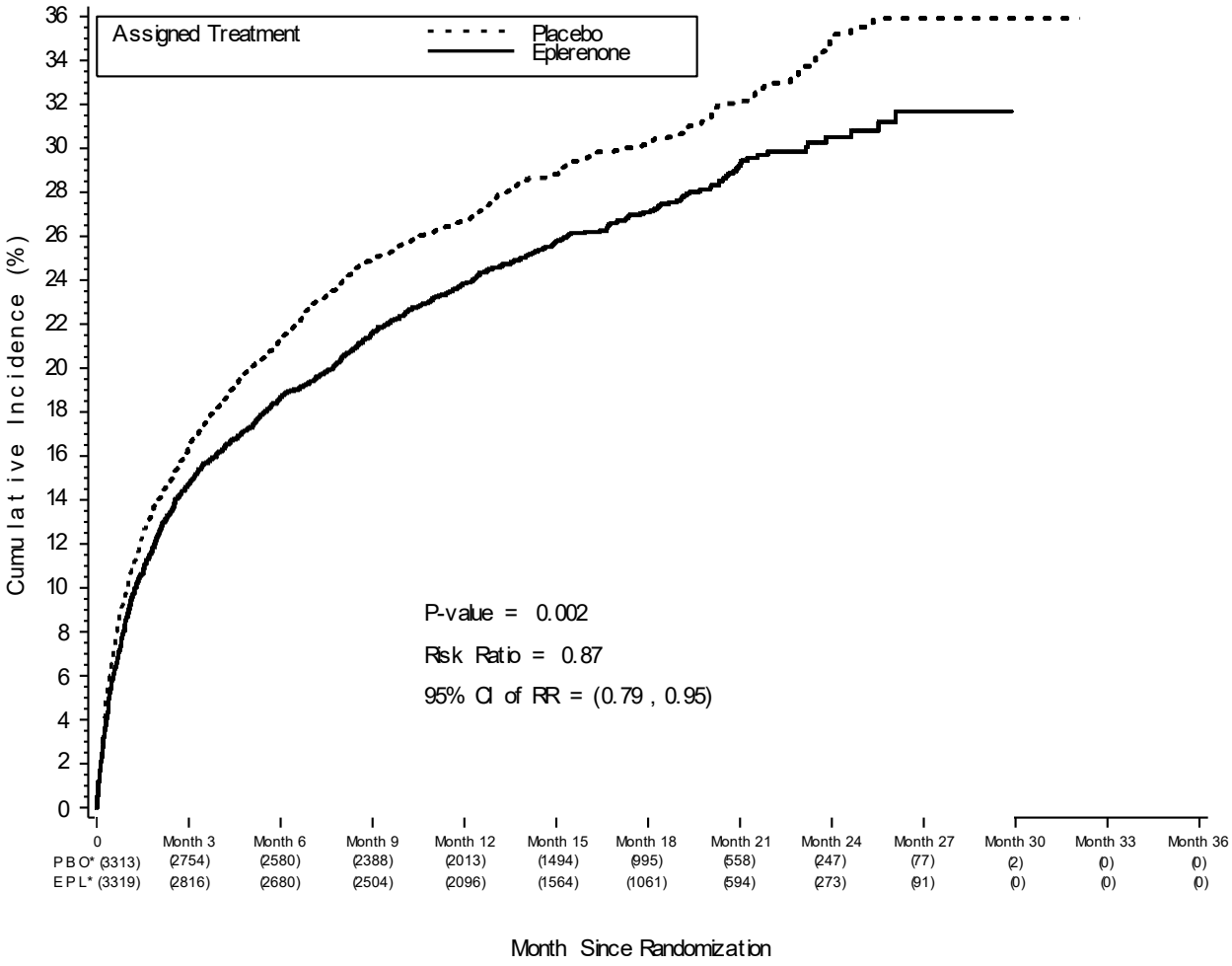
The time to first event for the second primary endpoint of CV death or hospitalization (defined as hospitalization for progression of HF, ventricular arrhythmias, acute MI or stroke), was longer in the eplerenone group (hazard ratio 0.87, 95% confidence interval 0.79 to 0.95, p = 0.002). An analysis that included the time to first occurrence of CV mortality and CV hospitalizations as defined above, as well as other causes of hospitalization showed a smaller effect with a hazard ratio of 0.92 (95% confidence interval 0.86 to 0.99; p = 0.028). The combined endpoints, including combined all-cause hospitalization and mortality, were driven primarily by CV mortality. Adjudicated nonfatal CV and non-CV events causing or prolonging hospitalization are shown in **Table 23**. Kaplan-Meier estimates for CV death or hospitalization are provided in **Figure 3**.

Table 23. Adjudicated Nonfatal Events Causing or Prolonging Hospitalization (Intent-to-Treat Population)

	Eplerenone 25-50 mg QD N=3319			Placebo N=3313		
	Incidence		Episodes	Incidence		Episodes
All hospitalizations	1493	(45.0%)	2815	1525	(46.0%)	2984
CV hospitalization - primary	606	(18.3%)	876	649	(19.6%)	1004
HF	345	(10.4%)	477	391	(11.8%)	618
Ventricular arrhythmias	52	(1.6%)	58	54	(1.6%)	63
Recurrent AMI	224	(6.7%)	268	229	(6.9%)	269
Stroke	70	(2.1%)	73	51	(1.5%)	54
CV hospitalization - other	917	(27.6%)	1389	925	(27.9%)	1450
Atrial fibrillation/flutter	86	(2.6%)	97	95	(2.9%)	107
Stable angina	89	(2.7%)	100	87	(2.6%)	100
Unstable angina	321	(9.7%)	404	307	(9.3%)	398
PVD	38	(1.1%)	47	32	(1.0%)	36
Hypotension	31	(0.9%)	34	29	(0.9%)	31
CV surgery	320	(9.6%)	348	301	(9.1%)	349
Other	318	(9.6%)	359	368	(11.1%)	429
Non-CV hospitalization	539	(16.2%)	745	559	(16.9%)	755
Pneumonia	35	(1.1%)	39	70	(2.1%)	74
COPD/COLD	17	(0.5%)	21	19	(0.6%)	23
Other pulmonary disease	28	(0.8%)	30	26	(0.8%)	27
Diabetes	28	(0.8%)	29	38	(1.1%)	38
Elective Surgery	65	(2.0%)	70	44	(1.3%)	48
Other	422	(12.7%)	556	420	(12.7%)	545

Incidence of hospitalization due to heart failure was 10.4% in the eplerenone group versus 11.8% in the placebo group (HR 0.85 [0.74-0.99]; 95% CI; P=0.03).

Figure 3. Cumulative Incidence of CV Mortality/Hospitalization



*: Number of Patients at risk.

In 616 eplerenone and 710 placebo patients ≥ 75 years of age, the subgroup analysis did not show a significant difference for all-cause mortality (HR=1.005; p=0.965).

Hypertension

A total of 3,299 patients were treated with eplerenone alone or in combination with other antihypertensive agents in clinical studies. These studies excluded patients with elevated baseline serum potassium (>5.0 mmol/L), elevated baseline serum creatinine generally >132 µmol/L in males and >115 µmol/L in females.

A 8-week, randomized, double-blind, multicenter, placebo-controlled, parallel group comparison trial was conducted in patients with baseline mild to moderate hypertension, seDBP of ≥ 95 mmHg and ≤ 114 mmHg. Patients received placebo, or eplerenone in doses of 25 mg twice daily, 50 mg once daily, and 50 mg twice daily. The adjusted mean change from baseline at each visit is shown in Table 24 and Table 25.

Table 24. Mean Change (±SD) from Baseline of Trough Sitting Diastolic Blood Pressure at Each Visit

	Placebo	Eplerenone 25 mg BID	Eplerenone 50 mg QD	Eplerenone 50 mg BID
Number of Patients	52	53	54	53
Week 2 (mmHg)	-4.9±7.68	-5.5±6.92	-4.5±8.07	-7.5±7.92
Week 4 (mmHg)	-3.9±7.50	-6.3±6.64	-5.7±7.27	-7.5±7.44
Week 8 (mmHg)	-1.3±6.93	-4.9±7.94	-4.4±7.77	-7.8±8.61

Table 25. Mean Change (±SD) from Baseline of Trough Sitting Systolic Blood Pressure* at Each Visit

	Placebo	Eplerenone 25 mg BID	Eplerenone 50 mg QD	Eplerenone 50 mg BID
Number of Patients	52	53	54	53
Week 2 (mmHg)	-5.5±11.26	-11.6±10.15	-7.1±12.51	-10.8±11.95
Week 4 (mmHg)	-3.2±13.95	-12.6±10.76	-8.0±15.77	-11.7±12.44
Week 8 (mmHg)	1.4±12.32	-8.9±13.63	-5.0±14.72	-11.8±16.55

*pre-specified secondary endpoint

The reductions in mean sitting DBP observed in the 3 eplerenone treatment groups at final study visit were statistically significantly different compared to placebo. Similarly, the statistically significant reductions in the 3 eplerenone treatment groups comparing to the placebo in mean sitting SBP (pre-specified secondary endpoint) at final visit are also detected.

DETAILED PHARMACOLOGY

Human Pharmacology

Pharmacokinetics

Absorption
Mean peak plasma concentrations of eplerenone are reached approximately 1.5 to 2 hours following oral administration. The absolute bioavailability of eplerenone is 69% following administration of a 100 mg oral tablet. Absorption is not affected by food. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 25 to 100 mg, and less than proportional at doses above 100 mg.

Distribution
Eplerenone is approximately 50% bound to plasma proteins, primarily to alpha 1-acid glycoprotein. The protein binding is concentration-independent within the expected therapeutic range of total plasma concentrations. The apparent volume of distribution at steady state ranges from 42 to 90 L. Eplerenone does not selectively partition into erythrocytes; the average ratio of plasma/whole blood concentrations is approximately 1.4:1.

Metabolism
Eplerenone is extensively metabolized in humans, and less than 5% of the dose is recovered unchanged in urine plus feces. Elimination of eplerenone involves Phase I metabolism, including hydroxylation of the methyl group to form several pharmacologically-inactive metabolites. Metabolites of eplerenone representing 5% or greater of the administered dose recovered in urine and feces are 6β-OH (primary metabolite), 6β-21-OH, 21-OH, 3α-6β-21-OH, and 3α-6β-OH. The 6β-OH, 6β-21-OH and 21-OH metabolites were the major metabolites of eplerenone recovered in the urine, representing approximately 28%, 13% and 5% of the dose, respectively. In vitro studies indicate that formation of the primary 6β-OH metabolite is predominantly mediated by CYP3A4. Plasma exposure of the 6β-OH metabolite is about 32% of the exposure of eplerenone in healthy adult subjects.

Excretion
Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted in the feces and approximately 67% was excreted in the urine. The elimination half-life of eplerenone is approximately 3 to 6 hours. The apparent plasma clearance is approximately 10 L/hr.

Special Populations and Conditions

Geriatrics
Healthy elderly subjects receiving eplerenone 100 mg QD for 12 days showed significantly higher plasma concentrations of eplerenone compared to healthy young adults. Mean steady-state C_{max} and AUC_{0-24} of eplerenone were 22% and 45% greater, respectively, for elderly subjects as compared to young subjects. Mean eplerenone AUC_{0-inf} after single-dose administration approximated steady-state AUC_{0-24} after QD dosing in both elderly and young subjects, suggesting the absence of time-dependent pharmacokinetics.

Pediatrics
A population pharmacokinetic model was developed to describe the single-dose pharmacokinetics of eplerenone in pediatric (2 to 16 years) and adult (≥ 18 years) hypertensive

patients. No covariates (age, body weight, body surface area, sex, or race) were found to influence apparent oral clearance (CL/F), and hence exposure (in terms of AUC) to eplerenone for a given dose would not be expected to differ between pediatric and adult patients. Body weight was found to be a significant covariate for apparent central volume of distribution (Vc/F). The peak concentration, C_{max}, which is influenced by Vc/F, was predicted to decrease by approximately 28% for each doubling of body weight. Overall, no differences between pediatric and adult patients were found that could not be explained by body weight.

Gender
The pharmacokinetics of eplerenone did not differ significantly between males and females.

Race
No statistically significant differences were found in mean steady-state AUC_{0-24}, C_{max}, and T_{max} of eplerenone between Black subjects and Caucasian subjects following a single oral 100 mg dose of eplerenone. Steady-state mean CL/F was 33% greater in Black than Caucasian subjects, resulting in a statistically insignificant 26% decrease in AUC_{0-24} in Blacks compared to Caucasians.

Results from healthy volunteer and patient studies indicate no significant difference in the pharmacokinetics of eplerenone between Japanese subjects and Caucasian subjects.

Renal Insufficiency
The single- and multiple-dose pharmacokinetics of eplerenone were evaluated in subjects with mild, moderate and severe renal impairment, in subjects with end-stage renal disease and in subjects with normal renal function.

Following single and multiple doses, eplerenone was generally readily absorbed, reaching maximum plasma concentrations within approximately 2 hours after dosing across all renal impairment groups. The $T_{1/2}$ for eplerenone was consistent across all groups, ranging from 4 to 6 hours. In patients with severe renal dysfunction, a 32% increase in steady state average AUC_{0-24} of eplerenone was observed as compared to age matched normal renal function control subjects. No apparent relationship was found between weight-normalized eplerenone CL/F and creatinine clearance among subjects with normal renal function and subjects with renal impairment, indicating that there was no correlation between eplerenone disposition kinetics and degree of renal dysfunction.

Based upon pharmacokinetic considerations alone, no dose adjustment is required in patients with varying degrees of renal impairment.

Hemodialysis removed only about 10% of the administered eplerenone dose from the systemic circulation. No dosage adjustment would be necessary for the hemodialysis procedure. Hemodialysis would not be expected to be a good method of removing eplerenone from the systemic circulation in case of overdosage.

Hepatic Insufficiency
The effect of moderate hepatic impairment (Child-Pugh Class B) on the single-dose and steady-state pharmacokinetics of eplerenone was evaluated. Compared to normal control subjects,

there was a 42% increase in mean eplerenone AUC_{0-24} after QD dosing in subjects with moderate hepatic impairment. No significant differences were found in mean steady-state C_{max} and T_{max} of eplerenone between subjects with moderate hepatic impairment and normal control subjects. Steady-state terminal $T_{1/2}$ of eplerenone was 8.1 hours for subjects with moderate hepatic impairment and 7.6 hours for normal control subjects.

The results of this study indicate that dose adjustment may not be required for patients with moderate (Child Pugh B) hepatic impairment based upon pharmacokinetic considerations alone. Patients with severe hepatic dysfunction were not studied and therefore, MINT-EPLERENONE is contraindicated in Child-Pugh C.

Pharmacokinetic Interaction Studies
An extensive in vitro evaluation of the metabolism-based drug interaction potential of eplerenone was conducted. The data indicate that it is unlikely that eplerenone will inhibit the metabolism of other drugs due to its high concentration causing 50% inhibition (IC50) [> 300 μM] against the major human CYP isoforms (1A2, 2C9, 2D6, 2C19, and 3A4). Drug-drug interactions based on P-glycoprotein mechanism are unlikely since eplerenone is not a substrate for, or an inhibitor of, the P-glycoprotein transporter.

Food consumption, concomitant antacid use, or consumption of double-strength grapefruit juice had no clinically important effects on the extent of eplerenone absorption when compared to administration of eplerenone tablets in a fasting state.

In vivo drug interaction studies focused on compounds that were known to be inhibitors, substrates, or inducers of CYP hepatic isoforms, specifically the CYP3A4 isozyme, or were substrates or inhibitors of P-glycoprotein.

Eplerenone (100 mg QD) has no clinically significant effect on the pharmacokinetics of glyburide, simvastatin, midazolam, cisapride, warfarin, cyclosporine, and oral contraceptives. Results indicate that eplerenone does not impact the metabolism of CYP3A4 or CYP2C9 substrates.

Coadministration of eplerenone (100 mg QD) with digoxin (200 mcg QD), a substrate for P-glycoprotein, did not produce any clinically significant changes in plasma exposure of digoxin.

Coadministration of eplerenone (100 mg QD) with St. John's Wort (300 mg TID for 14 days), an inducer of CYP3A4, lead to decreases in C_{max} (19%) and AUC_{0-inf} (31%), which are considered to be clinically insignificant.

The effect of a number of strong and moderate CYP3A4 inhibitors on the pharmacokinetics of eplerenone was evaluated. Coadministration of single 100 mg oral doses of eplerenone with ketoconazole (200 mg BID for 7 days) or fluconazole (200 mg QD for 7 days) resulted in statistically significant increases (441% and 123%, respectively) in total plasma exposure (AUC_{0-inf}) of eplerenone. Additionally, coadministration of erythromycin (500 mg BID) with eplerenone 100 mg QD for 7 days significantly increased total plasma exposure (187%) of eplerenone.
Coadministration of verapamil (240 mg QD) with eplerenone 100 mg QD for 7 days

significantly increased total plasma exposure (98%) and maximum plasma exposure (36%) of eplerenone.

Coadministration of saquinavir (1200 mg TID) with eplerenone 100 mg QD for 7 days significantly increased total plasma exposure (107%) of eplerenone.

Pharmacodynamics

Effects on Urinary Sodium and Potassium Excretion

The effect of eplerenone on urinary sodium and potassium excretion was evaluated in 3 single-dose studies and in 2 multiple-dose, dose-ranging studies.

The results of 2 single-dose studies showed increased urinary excretion of sodium and urinary log10 (Na^+/K^+) ratio in a dose-dependent manner following single-dose administration. Whereas, the other single dose study showed that there were no significantly high or low values of excreted sodium, Na^+/K^+ ratio or log10 Na^+/K^+ in urine 48 hours after administration.

Findings from one of the multiple-dose, dose-ranging study showed that these increases in urinary excretion of sodium and urinary log10 (Na^+/K^+) ratio were not sustained after multiple dosing, while the other multiple-dose, dose-ranging study, only slight increases were observed in these parameters.

Other Pharmacodynamic Assessments

The effects of eplerenone on plasma renin activity, plasma aldosterone and plasma hormones were assessed in 2 studies. The results showed that in one study, no significantly high or low values of changes in these parameters were observed in any of the non-fasting groups. In the other study, obvious increases in plasma aldosterone concentration and plasma renin activity were not noted, however, as the values in the eplerenone group were apparently higher than those in the placebo group, a pharmacological action of eplerenone was suggested.

Electrocardiographic Interval Analyses

The effects of eplerenone on ECG interval durations were retrospectively evaluated in 5 clinical pharmacology studies. The results of the ECG analyses were uniform across the 5 studies and indicated that there was no effect of eplerenone on any ECG parameter, most notably the QTc interval. The results of the studies suggest that eplerenone is devoid of any ECG effects and should not pose any safety concern in regards to cardiac repolarization effects.

The electrocardiographic effects of eplerenone as compared to amlodipine were further evaluated by ambulatory ECG (Holter) monitoring in a cohort of patients with mild to moderate hypertension. There were no differences between eplerenone and amlodipine on ventricular repolarization as assessed by QT interval analysis. Within the eplerenone group, no changes from baseline were apparent from the QTc interval analysis.

Animal Pharmacology

Heart Failure

Nonclinical studies suggest that aldosterone acts directly on the cardiac MR to produce deleterious effects such as cardiac hypertrophy and fibrosis. Nonclinical studies using eplerenone provide additional support for this hypothesis. For example, eplerenone inhibits non- genomic actions of aldosterone in cardiomyocytes and reduces left ventricular hypertrophy (LVH) in rats with pressure-overload-induced hypertrophy resulting from aortic banding.

Further support for the cardioprotective effect of direct blockade of MR in the heart was obtained from studies in experimental models of heart failure (HF). Evaluation of eplerenone efficacy in diverse models of HF demonstrated that selective aldosterone blockade effectively attenuates HF development, improves left ventricular function, and reduces LVH independent of HF etiology and in the absence of hemodynamic effects. Moreover, the benefit was achieved when eplerenone was administered prior to HF or during disease progression. In addition, cardioprotection may result from direct actions of eplerenone on the myocardium, as efficacy was accompanied by a reduction in cardiac gelatinase activity, cardiomyocyte cross-sectional area, and reduced expression of proinflammatory and hypertrophy marker genes.

The Eplerenone Efficacy in Experimental Models of Heart Failure is presented in **Table 25.**

Table 25. Eplerenone Efficacy in Experimental Models of Heart Failure

Model	Eplerenone Dose	Treatment	Enalapril Dose	Eplerenone Efficacy
Transgenic mice overexpressing cardiac 11β HSD2	~200 mg/kg/day, chow	1 - 3.5 mo of age		↑ EF 16%* and normalization of EDV and ESV ↓ Expression of LVH and inflammatory marker genes (βMHC, ANP,Collagen I, OPN)
Post-MI Rat	300 mg/kg/day, b.i.d., gavage	3, 7, or 28 days post-MI		No significant impact on infarct healing
Post-MI Rat	~100 mg/kg/day, chow	8 weeks post-MI	10 mg/kg/day, in water	Eplerenone, Enalapril, and Co-administration therapy: ↑ EF (Epl ↑ EF 7%†) ↓ LVAd, LVAs Eplerenone did not change SBP Enalapril ↓ SBP
Post-MI Mouse	~200 mg/kg/day, chow	2 - 14 weeks post-MI	20 mg/kg/day, in water	Eplerenone, Enalapril, and Co-administration therapy: ↑ EF (Epl ↑ EF 11%†) ↓ LVAs, MCSA, ICF Eplerenone did not change SBP Enalapril ↓ SBP
Canine Microembolism HF model	20 mg/kg/day, b.i.d., oral	3 months starting at EF ≤ 40%		EF ↑ 6%‡ and prevention of LV dilation as measured by preserved EDV and ESV ↓ Cardiac gelatinase activity, MCSA, ICF Eplerenone did not change SBP, HR, or SVR

Model	Eplerenone Dose	Treatment	Enalapril Dose	Eplerenone Efficacy
SHHF	~ 100 mg/kg/day, chow	14 - 17 mo of age	10 mg/kg/day, in water	Eplerenone + Enalapril Co-administration: Maintained EF and prevented LV dilation as measured by LVAs and LVAd ↓Cardiac and renal inflammatory marker gene expression (OPN, MCP-1, IL-1, IL-6)
SHHF	~ 100 mg/kg/day , chow	3.5 - 17.5 mo of age		EF ↑ 12%‡ ↓ LVAs and LVAd

* p < 0.05 vs. Transgenic Control Mice; †, p < 0.05 vs. Untreated Post-MI animals; ‡ p < 0.05 vs. Untreated animals. EF, Ejection Fraction; LVAd, Left Ventricular Area at Diastole; LVAs, Left Ventricular Area at Systole; EDV, End Diastolic Volume; ESV, End Systolic Volume; bMHC, beta MyosinHeavy Chain; ANP, Atrial Natriuretic Peptide; OPN, Osteopontin; SBP, SystolicBlood Pressure; MCSA, Myocyte Cross-Sectional Area; ICF, Interstitial Collagen Fraction; HR, Heart Rate; SVR, Systemic Vascular Resistance; MCP-1, Monocyte Chemoattractant Protein-1; IL-1, Interleukin-1; IL-6, Interleukin-6.

TOXICOLOGY

The nonclinical safety assessment of eplerenone comprised studies of acute and repeat-dose toxicity in mice, rats and dogs, in vivo and in vitro genotoxicity, carcinogenicity in rats and mice, reproductive toxicity in rats and rabbits, and in vivo and in vitro mechanistic studies designed to clarify specific findings. The major toxic endpoints of the pivotal repeat-dose studies in animals are summarized in **Table 26**.

Table 26. Outcomes of Pivotal In Vivo Toxicity Studies

Species and Study Type	Major Endpoint	Threshold Dosage mg/kg/day	NOAEL* mg/kg/day	Animal:Human $AUC_{(0\text{-}24\ h)}$ Exposure Multiple at NOAEL*
Mouse Repeat-Dose Toxicity 13-Wk	None	NA	1000	8x
Rat Repeat-Dose Toxicity 13- and 26-Wk and 52-Wk interim in 2-Yr Carcinogenicity	Kidney- chronic progressive nephropathy	•500 for 13 weeks •250 for 1 year	•100 Females •200 Males	4.5x Males and Females
Dog Repeat-Dose Toxicity 13- and 52-Wk	•Males-Prostate atrophy •Males and Females- Electrolyte imbalance, overt toxicity	•15 Males •300 Both sexes	•5 Males •100 Both sexes	•2x Males •19x Females
Mouse Carcinogenicity 26-Wk	None	NA	1000	9x
Rat Carcinogenicity 2-Year	Thyroid- benign follicular cell adenoma	•75 Males •250 Females	•20 Males •75 Females	•0.6x Males •5x Females
Rat Fertility and Embryo Development	•Males-Decreased seminal vesicle and epididymis weights and increased pre-implantation loss •Females-None	1000 Males	•300 Males •1000 Females	•8x Males •31x Females (estimated)
Rat Embryo-Fetal Development	•Females (dams)-Decreased feed consumption and body weight •Fetuses-Decreased body weights, no developmental abnormalities	•300 Females (dams) •1000 Fetuses	•100 Females (dams) •300 Fetuses	•Exposure to dams at fetal NOAEL: 31x Gestation Day 6 •15x Gestation Day 17
Rat Pre- and Post-natal Development	•Females (dams)-Decreased feed consumption and body weight •Offspring-Decreased body weights at birth, no post-natal effects	1000 Females (dams) and offspring	300 Females (dams) and offspring	15x Females (Dams) (estimated)

Species and Study Type	Major Endpoint	Threshold Dosage mg/kg/day	NOAEL* mg/kg/day	Animal:Human $AUC_{(0\text{-}24\ h)}$ Exposure Multiple at NOAEL*
Rabbit Embryo-fetal Development	•Females (dams)-Decreased feed consumption and body weight •Fetuses-Increased resorptions, no developmental abnormalities	300 Females (dams) and fetuses	100 Females (dams) and fetuses	Females (Dams): 9x on Gestation Days 7 and 19

NOAEL = no-observed-adverse-effect level

Acute Toxicity

Eplerenone had a low level of acute toxicity in animals. It caused severe clinical signs and/or deaths only at high doses in the mouse (≥1500 mg/kg) and the dog (≥500 mg/kg), but not in the rat (up to 2000 mg/kg).

Repeat-Dose Toxicity

In repeat-dose animal toxicity studies, the principal adverse effects of eplerenone were an increase in the incidence and/or severity of chronic progressive nephropathy (CPN), which is a rat-specific kidney disease having no human counterpart, and reversible prostate atrophy in the male dog. Neither of these is considered to represent a significant human hazard, and they occur only at multiples of the human therapeutic exposure (~ 12-fold higher for rats and 7-fold higher for dogs compared to the area under the concentration-time curve for humans taking 100 mg). Eplerenone also caused pharmacologically mediated reversible changes, such as increased serum aldosterone, increased urinary sodium to potassium ratio, and/or hypertrophy of the zona glomerulosa of the adrenal cortex. Certain other changes in rodents, such as increased serum cholesterol, triglycerides and protein, and secondary thyrotrophic effects, were considered to be physiological adaptations related to hepatic enzyme induction and the associated increased liver mass.

Carcinogenicity and Genotoxicity Studies

Eplerenone was not genotoxic in an extensive battery of in vitro and in vivo tests. Eplerenone was not carcinogenic in heterozygous p53 knock-out mice, a strain that is highly susceptible to genotoxic carcinogens. When tissues from a 2-year rat carcinogenesis study were examined by standard histolopathological methods, eplerenone produced only benign thyroid follicular cell adenomas by a mechanism related to increased hepatic clearance of thyroid-stimulating hormone. This mechanism is considered to be irrelevant to humans. When an extended histopathological evaluation of rat kidneys was conducted, female rats, at the highest dose tested (250 mg/kg/day), were found to have an increased incidence of benign renal tubular cell adenomas. The increased incidence was highly correlated to an increased severity of CPN in these rats. As indicated previously, CPN has no human counterpart and its increased severity in rats is not considered to represent a hazard for human health.

There was no drug-related tumor response in heterozygous P53 deficient mice when tested for 6 months at dosages up to 1000 mg/kg/day (systemic AUC exposures up to 9 times the exposure in humans receiving the 100 mg/day therapeutic dose). Statistically significant increases in benign thyroid tumors were observed after 2 years in both male and female rats when administered eplerenone 250 mg/kg/day (highest dose tested), and in male rats only at 75 mg/kg/day. These dosages provided systemic AUC exposures approximately 2 to 12 times higher than the average human therapeutic exposure at 100 mg/day. Repeat dose administration of eplerenone to rats increases the hepatic conjugation and clearance of thyroxin, which results in increased levels of thyroid stimulating hormone (TSH) by a

compensatory mechanism. Drugs that have produced thyroid tumors by this rodent-specific mechanism have not shown a similar effect in humans.

Reproductive and Teratogenicity Studies

There was no evidence of eplerenone related teratogenicity in rats or rabbits. Fertility was not affected in female rats. Male rats showed only a slight decrease in fertility at a highly exaggerated dose (1000 mg/kg/day). This is considered to be secondary to decreased size of seminal plugs, a mechanism that is irrelevant to humans.

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PART III: CONSUMER INFORMATION

PrMINT-EPLERENONE
Eplerenone Tablets
25 mg and 50 mg

This leaflet is Part III of a three-part "Product Monograph" published when MINT-EPLERENONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MINT-EPLERENONE. Contact your doctor or pharmacist if you have any questions about the drug. Please read this information carefully.

ABOUT THIS MEDICATION

What the medication is used for:

In adults, MINT-EPLERENONE is used alone or combined with other drugs for patients with hypertension (high blood pressure) to lower blood pressure.

In adults, MINT-EPLERENONE is used in combination with other drugs for patients with heart failure:

- to prevent worsening heart failure
- to prevent death from heart failure
- to reduce the risk of hospitalizations for heart failure

If you are an adult under 75 years old with heart failure, MINT-EPLERENONE may reduce the risk of death. This is not necessarily true for patients 75 years old and older.

What it does:

Your body makes a substance called aldosterone. It is important for controlling blood pressure and heart function. Sometimes, high levels of aldosterone can cause changes in your body that may worsen heart failure. MINT-EPLERENONE works by blocking the actions of aldosterone, and can help prevent heart failure from getting worse.

When it should not be used:

Do not use MINT-EPLERENONE if you:

- are hypersensitive (allergic) to eplerenone or to any of the other ingredients of MINT-EPLERENONE (see below for the non-medicinal ingredients);
- have high levels of potassium in your blood;
- are taking potassium sparing diuretics (certain types of water tablets);
- have severe liver impairment;
- have heart failure and severe kidney impairment;
- have hypertension and moderate kidney impairment
- are taking other medications that may affect the
- elimination of MINT-EPLERENONE, such as:
  - ritonavir or nelfinavir (antiviral medication for treating HIV);
  - clarithromycin, or telithromycin (antibiotics used to treat bacterial infections);
  - ketoconazole or itraconazole (medicines that are used to treat fungal infections);
  - nefazadone (used to treat depression);
  - potassium supplements.

What the medicinal ingredient is:

Eplerenone

What the nonmedicinal ingredients are:

- croscarmellose sodium
- D&C Yellow #10 Aluminum Lake
- FD&C Yellow#6 Aluminum Lake
- hydroxypropyl methylcellulose
- iron oxide red
- iron oxide yellow
- lactose monohydrate
- magnesium stearate
- microcrystalline cellulose
- polyethylene glycol
- polysorbate 80
- sodium lauryl sulphate
- talc
- titanium dioxide

What dosage forms it comes in:

MINT-EPLERENONE tablets are available in 25 mg and 50 mg strengths.

WARNINGS AND PRECAUTIONS

BEFORE you use MINT-EPLERENONE tell your doctor or pharmacist if:

- you are pregnant or if you are planning to become pregnant. The effects of MINT-EPLERENONE have not been evaluated during pregnancy. Ask your doctor or pharmacist for advice before taking any medicine.
- you are breast-feeding or intend to breast-feed;
- you have kidney or liver disease;
- you are diabetic;
- you are taking lithium (usually given as a mood stabilizing medication);
- you are using potassium supplements or salt substitutes containing potassium.

Please contact your doctor if you are taking any of the above medicines, or have taken them in the past.

You may feel dizzy after taking this medicine. If this happens, tell your doctor about it and do not drive or operate machinery.

INTERACTIONS WITH THIS MEDICATION

Certain medications can affect the way that MINT-EPLERENONE is broken down by the body. Interaction with other drugs is possible. Please inform your doctor if you are taking any of the following medicines (see also "When it should not be used"):

- ketoconazole, itraconazole or fluconazole (used to treat fungal infections);
- verapamil or diltiazem (used for heart problems and/or high blood pressure);
- digoxin or amiodarone (used to treat particular heart conditions including irregular heart rhythms);
- angiotensin converting enzyme inhibitors which are any medication with generic names ending with “pril” (used for high blood pressure or heart conditions);
- angiotensin II receptor antagonists, which are any medication with generic names ending with “sartan” (used for high blood pressure, or particular kidney conditions);
- potassium sparing diuretics (certain water tablets used to treat fluid retention) (see also "When it should not be used");
- potassium supplements (salt tablets);
- herbal preparations containing large amounts of potassium (such as Noni fruit or juice, dandelion);
- saquinavir, ritonavir or nelfinavir (antiviral medication for treating HIV);
- erythromycin, clarithromycin, telithromycin, or rifampicin (antibiotics used to treat bacterial infections);
- lithium (usually given as a mood stabilizing medication);
- nefazadone and St John's Wort (used to treat depression);
- carbamazepine, phenytoin and phenobarbital (used to treat epilepsy);
- Non-steroidal anti-inflammatory drugs (certain pain killers, such as ibuprofen and other pain relievers).

Tell your doctor or pharmacist if you are taking any other medications, including prescription, non-prescription and natural health products.

PROPER USE OF THIS MEDICATION

Your doctor and pharmacist will tell you how to take your medicine. Carefully follow the instructions given to you by your doctor and pharmacist.

MINT-EPLERENONE tablets may be taken with or after a meal or on an empty stomach. Swallow the tablets with a glass of water without chewing.

MINT-EPLERENONE is not recommended for children.

Usual dose:

The usual starting dose will depend on the potassium level in your body and your kidney condition which will be assessed by your doctor.

In people with normal or near normal kidney function, *for heart failure* the usual starting dose is one 25 mg tablet once daily, increasing to one 50 mg tablet once daily in about 4 weeks, as instructed by your doctor. *For hypertension*, the usual dose is 50 mg tablet once daily.

The maximum daily dose for heart failure is 50 mg and for hypertension, it is 100 mg.

Lower doses will be used in people with elevated potassium in the blood or weaker kidney function.

Blood potassium levels should be measured before starting MINT-EPLERENONE therapy, within the first week and at one month after the start of treatment or after a change in dose. The dose may be adjusted by your doctor, depending on the potassium levels in your blood. It is very important that you comply with your doctor's recommendations particularly regarding the laboratory test which may be prescribed.

It is important to keep taking MINT-EPLERENONE as prescribed unless your doctor tells you to stop your treatment.

Overdose:

If you take more MINT-EPLERENONE than you should, tell your doctor or pharmacist immediately.

If you think you have taken too much MINT-EPLERENONE contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a tablet take it as soon as you remember. If it is almost time to take the next tablet, do not take the tablet you have missed. Instead, take the next tablet when it is due and afterwards, continue to take your tablets as your doctor has prescribed for you. Do not take a double dose to make up for the forgotten tablet.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include headache. The most common side effects seen with eplerenone are related to increased blood potassium levels.

MINT-EPLERENONE can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	**Increased levels of potassium in the blood:** Irregular heartbeats, muscle weakness and generally feeling unwell		✓	
Uncommon	**Dehydration:** headaches, dizziness or fainting	✓		
	Blood clot in the leg (arterial leg thrombosis): swelling, pain and redness in a leg that can be warm to touch.		✓	
	Low Blood Pressure: feeling of lightheadedness or fainting especially when getting up from a lying or sitting position	✓		
	Hypothyroidism: constipation, weight gain, fatigue, intolerance to cold	✓		
	Gastroesophageal reflux disease (GERD): heartburn, regurgitation and trouble swallowing	✓		
	Pancreatitis (inflammation of the pancreas): abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓	
	chest pain		✓	
	angina		✓	
	breathing difficulty		✓	
	changes in rhythm or pace of heart beat		✓	
	less urine than is normal for you		✓	
	swelling of the hands, feet, ankles, face, lips, mouth, or throat (may cause difficulty in swallowing or breathing)			✓
	hives		✓	
	fainting		✓	
	yellowing of the skin and eyes, also called jaundice		✓	
	weight gain		✓	

This is not a complete list of side effects. For any unexpected effects while taking MINT-EPLERENONE, contact your doctor or pharmacist.

HOW TO STORE IT

Always keep medicine well out of sight and reach of children. Store at controlled room temperature (15–30ºC).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to the Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Call toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about MINT-EPLERENONE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp; the manufacturer's website, *www.mintpharmaceuticals.com* or by calling 1-877-398-9696.

This leaflet was prepared by Mint Pharmaceuticals Inc.

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