Epleron®

Eplerenone

FILM COATED TABLET

DESCRIPTION

Epleron® 25 Film-Coated Tablet :

Brown film-coated tablet with logo  and plain on the other side.

Epleron® 50 Film-Coated Tablet :

Brown film-coated tablet with logo  and plain on the other side.

COMPOSITION

Epleron® 25 Film-Coated Tablet : Each film coated tablet contains Eplerenone 25 mg

Epleron® 50 Film-Coated Tablet : Each film coated tablet contains Eplerenone 50 mg

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group : Aldosterone antagonist, ATC Code : C03DA04

1.1 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.

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

1.2 Pharmacodynamics

There was no significant change in average heart rate among patients treated with eplerenone in the combined clinical studies. 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.

1.3 Pharmacokinetics

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 CYP3A (e.g., ketoconazole, saquinavir) 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. Absorption is not affected by food. The absolute bioavailability of eplerenone is 69% following administration of a 100 mg oral tablet. Both peak plasma levels (Cmax) and area under the curve (AUC) are dose proportional for doses of 25 mg to

100 mg and less than proportional at doses above 100 mg. Upon repeat dosing, steady state levels are reached within 2 days.
The plasma protein binding of eplerenone is about 50% and it is primarily bound to alpha 1-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.
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. At steady state, elderly subjects had increases in Cmax (22%) and AUC (45%) compared with younger subjects (18 to 45 years). The pharmacokinetics of eplerenone did not differ significantly between males and females. At steady state, Cmax was 19% lower and AUC was 26% lower in Blacks [see Dosage and Administration and Use in Specific Populations].
Renal Impairment
The pharmacokinetics of eplerenone was evaluated in patients with varying degrees of renal impairment and in patients undergoing hemodialysis. Compared with control subjects, steady state AUC and Cmax 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].
Hepatic Impairment
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 Cmax and AUC of eplerenone were increased by 3.6% and 42%, respectively.
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 Cmax in patients with stable heart failure were 38% and 30% higher, respectively.

CLINICAL STUDIES
Clinical studies conducted using INSPRA® tablets as the Innovator
1. Heart Failure Post-Myocardial Infarction
The eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS) was a multinational, multicenter, double-blind, randomized, placebo-controlled study in patients clinically stable 3 to 14 days after an acute MI with LV dysfunction (as measured by left ventricular ejection fraction [LVEF] ≤40%) and either diabetes or clinical evidence of HF (pulmonary congestion by exam or chest x-ray or S3). Patients with HF of valvular or congenital etiology, patients with unstable post-infarct angina, and patients with serum potassium >5.0 mEq/L or serum creatinine >2.5 mg/dL were 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 mEq/L. Dosage was reduced or suspended anytime during the study if serum potassium levels were ≥5.5 mEq/L [see Dosage and Administration].

EPHESUS randomized 6,632 patients (9.3% U.S.) at 671 centers in 27 countries. The study population was primarily white (90%, with 1% Black, 1% Asian, 6% Hispanic, 2% other) and male (71%). The mean age was 64 years (range, 22 to 94 years). The majority of patients had pulmonary congestion (75%) by exam or x-ray and was 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%), beta-blockers (83%), nitrates (72%), loop diuretics (66%), or HMG-CoA reductase inhibitors (60%).

Patients were followed for an average of 16 months (range, 0 to 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 mortality [defined as sudden cardiac death or death due to progression of HF, stroke, or other CV causes] or CV hospitalization (defined as hospitalization for progression of HF, ventricular arrhythmias, acute MI, or stroke).

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 1 and the components of mortality are provided in Table 5.

Figure 1. Kapla-Meier Estimates of All-Cause Mortality

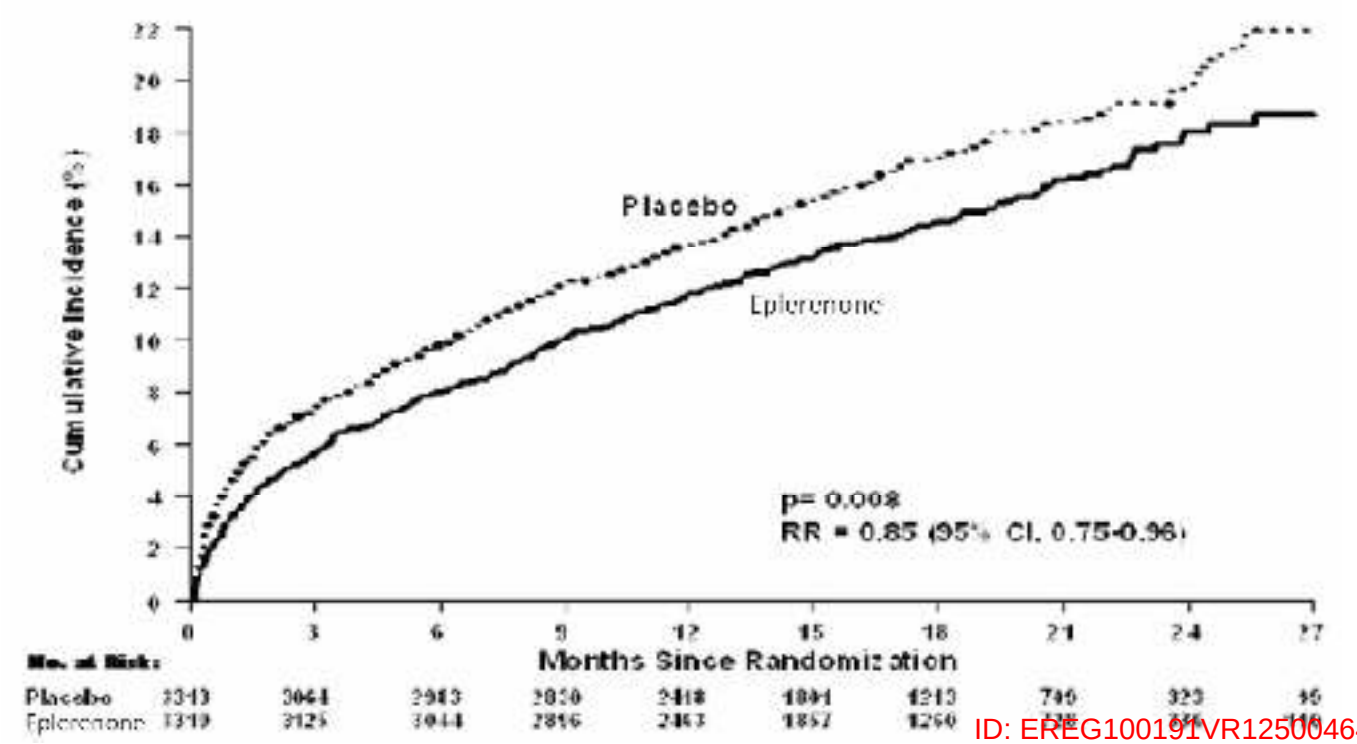


Table 5. Components of All-cause Mortality in EPHESUS

	Eplerenone (N=3319) n (%)	Placebo (N=3313) n (%)	Hazard Ratio	p-value
Death from any cause	478 (14.4)	554 (16.7%)	0.85	0.008
CV Death	407 (12.3)	483 (14.6%)	0.83	0.005
Non-CV Death	60 (1.8)	54 (1.6)		
Unknown or unwitnessed death	11 (0.3)	17 (0.5)		

Most CV deaths were attributed to sudden death, acute MI, and HF.
The time to first event for the co-primary endpoint of CV death or hospitalization, as defined above, 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 all CV hospitalizations (atrial arrhythmia, angina, CV procedures, progression of HF, MI, stroke, ventricular arrhythmia, or other CV causes) 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. The combined endpoints in EPHESUS, including all-cause hospitalization and all-cause mortality, are presented in Table 6.

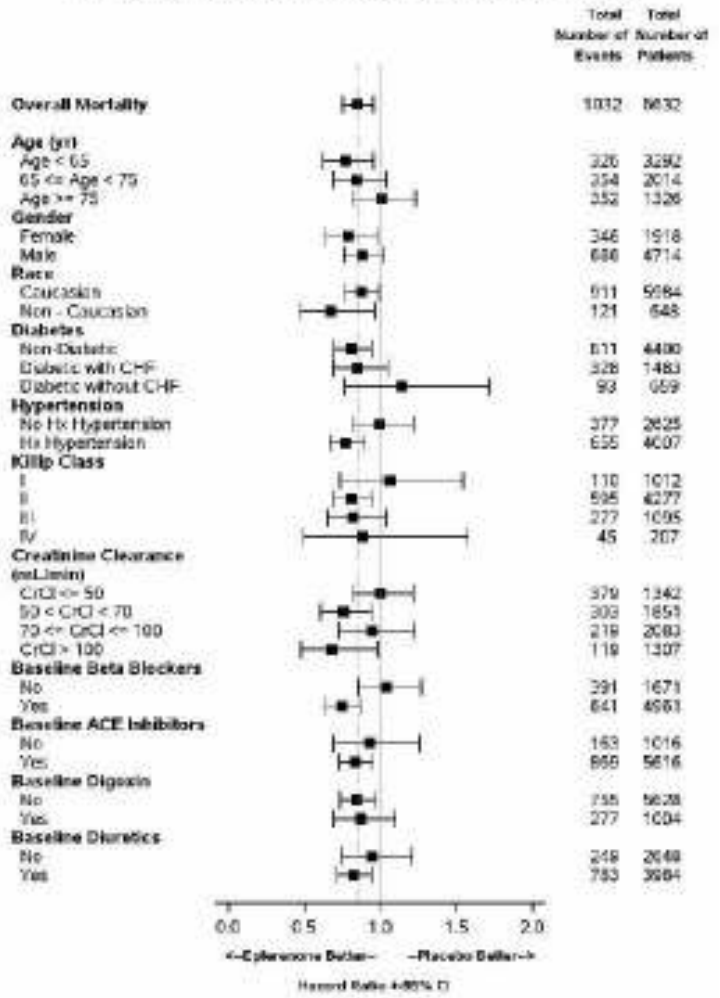
Table 6. Rates of death or hospitalization in EPHESUS

Event	**Eplerenone n (%)**	**Placebo n (%)**
CV death or hospitalization for progression of HF, stroke, MI or ventricular arrhythmia[1]	885 (26.7)	993 (30.0)
Death	407 (12.3)	483 (14.6)
Hospitalization	606 (18.3)	649 (19.6)
CV death or hospitalization for progression of HF, stroke, MI, ventricular arrhythmia, atrial arrhythmia, angina, CV procedures, or other CV causes (PVD; Hypotension)	1516 (45.7)	1610 (48.6)
Death	407 (12.3)	483 (14.6)
Hospitalization	1281 (38.6)	1307 (39.5)
All-cause death or hospitalization	1734 (52.2)	1833 (55.3)
Death[1]	478 (14.4)	554 (16.7)
Hospitalization	1497 (45.1)	1530 (46.2)

[1]Co-Primary Endpoint

Mortality hazard ratios varied for some subgroups in Figure 2. Mortality hazard ratios appeared favorable for eplerenone for both genders and for all races or ethnic groups, although the numbers of non-Caucasians were low (648, 10%). Patients with diabetes without clinical evidence of HF and patients greater than 75 years did not appear to benefit from the use of eplerenone. Such subgroup analyses must be interpreted cautiously.

Figure 2. Hazard Ratios of All-Cause Mortality by Subgroups



Analyses conducted for a variety of CV biomarkers did not confirm a mechanism of action by which mortality was reduced.

2. Hypertension

The safety and efficacy of eplerenone have been evaluated alone and in combination with other antihypertensive agents in clinical studies of 3091 hypertensive patients. The studies included 46% women, 14% Blacks, and 22% elderly (age ≥65). The studies excluded patients with elevated baseline serum potassium (>5.0 mEq/L) and elevated baseline serum creatinine (generally >1.5 mg/dL in males and >1.3 mg/dL in females).

Two fixed-dose, placebo-controlled, 8-to 12-week monotherapy studies in patients with baseline diastolic blood pressures of 95 to 114 mm Hg were conducted to assess the antihypertensive effect of eplerenone. In these two studies, 611 patients were randomized to eplerenone and 140 patients to placebo. Patients received eplerenone in doses of 25 mg to 400 mg daily as either a single daily dose or divided into two daily doses. The mean placebo-subtracted reductions in trough cuff blood pressure achieved by eplerenone in these studies at doses up to 200 mg are shown in Figures 3 and 4.

Figure 3. Eplerenone Dose Response - Through Cuff SBP Placebo-Substracted Adjusted Mean Change from Baseline in Hypertension Studies

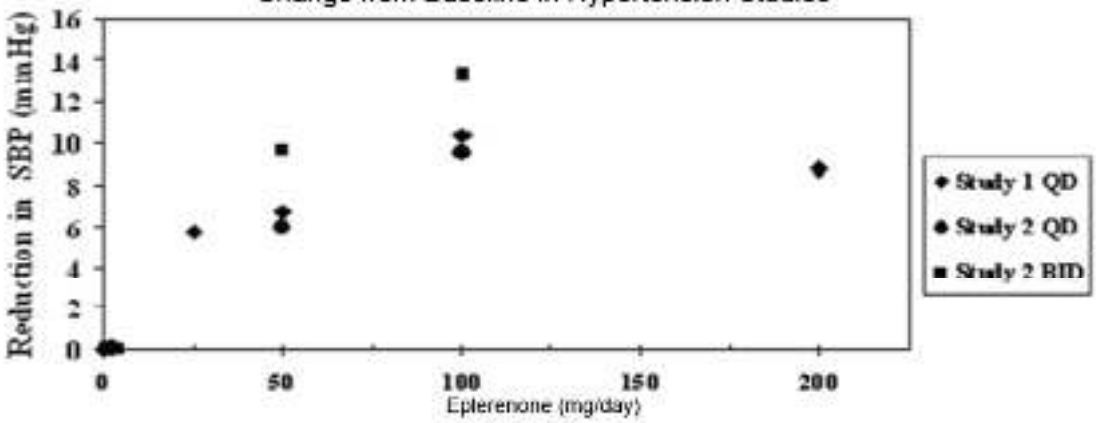
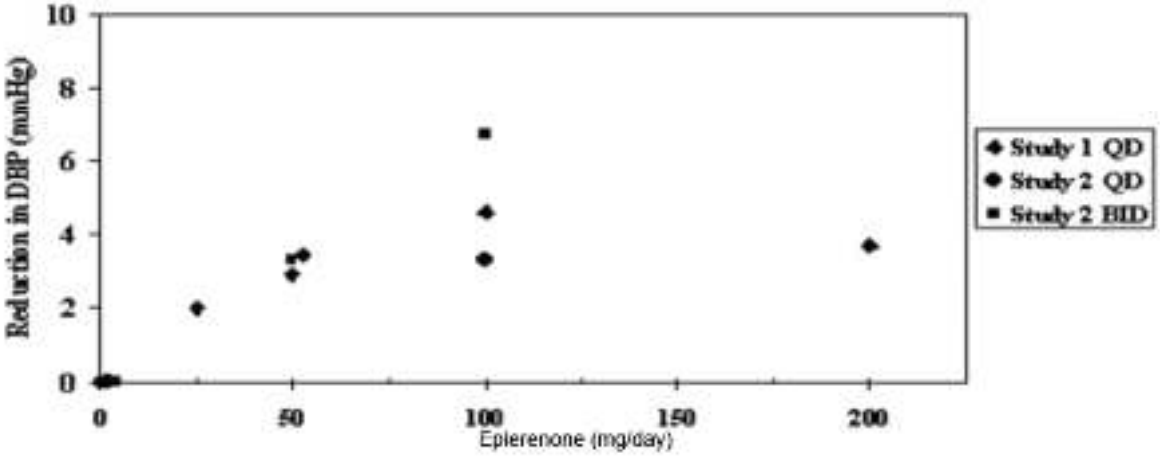


Figure 4. Eplerenone Dose Response - Through Cuff DBP Placebo-Substracted Adjusted Mean Change from Baseline in Hypertension Studies



Patients treated with Eplerenone 50 mg to 200 mg daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough with differences from placebo of 6–13 mm Hg (systolic) and 3–7 mm Hg (diastolic). These effects were confirmed by assessments with 24-hour ambulatory blood pressure monitoring (ABPM). In these studies, assessments of 24-hour ABPM data demonstrated that Eplerenone, administered once or twice daily, maintained antihypertensive efficacy over the entire dosing interval. However, at a total daily dose of 100 mg, Eplerenone administered as 50 mg twice per day produced greater trough cuff (4/3 mm Hg) and ABPM (2/1 mm Hg) blood pressure reductions than 100 mg given once daily.

Blood pressure lowering was apparent within 2 weeks from the start of therapy with Eplerenone, with maximal antihypertensive effects achieved within 4 weeks. Stopping Eplerenone following treatment for 8 to 24 weeks in six studies did not lead to adverse event rates in the week following withdrawal of Eplerenone greater than following placebo or active control withdrawal. Blood pressures in patients not taking other antihypertensives rose 1 week after withdrawal of Eplerenone by about 6/3 mm Hg, suggesting that the antihypertensive effect of Eplerenone was maintained through 8 to 24 weeks.

Blood pressure reductions with Eplerenone in the two fixed-dose monotherapy studies and other studies using titrated doses, as well as concomitant treatments, were not significantly different when analyzed by age, gender, or race with one exception. In a study in patients

with low renin hypertension, blood pressure reductions in Blacks were smaller than those in whites during the initial titration period with Eplerenone.
Eplerenone has been studied concomitantly with treatment with ACE inhibitors, ARB, calcium channel blockers, beta-blockers, and hydrochlorothiazide. When administered concomitantly with one of these drugs eplerenone usually produced its expected antihypertensive effects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Eplerenone was non-genotoxic in a battery of assays including in vitro bacterial mutagenesis (Ames test in Salmonella spp. and E. Coli), in vitro mammalian cell mutagenesis (mouse lymphoma cells), in vitro chromosomal aberration (Chinese hamster ovary cells), in vivo rat bone marrow micronucleus formation, and in vivo/ex vivo unscheduled DNA synthesis in rat liver.
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 TSH by a compensatory mechanism. Drugs that have produced thyroid tumors by this rodent-specific mechanism have not shown a similar effect in humans.
Male rats treated with eplerenone at 1000 mg/kg/day for 10 weeks (AUC 17 times that at the 100 mg/day human therapeutic dose) had decreased weights of seminal vesicles and epididymides and slightly decreased fertility. Dogs administered eplerenone at dosages of 15 mg/kg/day and higher (AUC 5 times that at the 100 mg/day human therapeutic dose) had dose-related prostate atrophy. The prostate atrophy was reversible after daily treatment for 1 year at 100 mg/kg/day. Dogs with prostate atrophy showed no decline in libido, sexual performance, or semen quality. Testicular weight and histology were not affected by eplerenone in any test animal species at any dosage.

INDICATIONS

Eplerenone is indicated for :

- The treatment of symptomatic heart failure, in addition to standard theraphy including beta-blockers, in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction.
- The treatment of mild to moderate hypertension, to lower blood pressure. Eplerenone may be used alone but usually in combination with other antihypertensive agents.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

1. Symptomatic Heart Failure and Heart Failure After Recent Myocardial Infarction

Initiate treatment at 25 mg once daily and titrate to the recommended dose of 50 mg once daily, preferably within 4 weeks as tolerated by the patient.

Once treatment with Eplerenone has begun, adjust the dose based on the serum potassium level as shown in Table 1.

Table 1. Dose Adjustment in Heart Failure Post-MI

Serum Potassium (mEq/L)	Dose Adjustment
<5.0	25 mg every other day to 25 mg once daily 25 mg once daily to 50 mg once daily
5.0–5.4	No adjustment
5.5–5.9	50 mg once daily to 25 mg once daily 25 mg once daily to 25 mg every other day 25 mg every other day to withhold
≥6.0	Withhold and restart at 25 mg every other day when potassium levels fall to <5.5 mEq/L

2. Hypertension

The recommended starting dose of Eplerenone is 50 mg administered once daily. The full therapeutic effect of Eplerenone is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50 mg once daily increase the dosage of Eplerenone to 50 mg twice daily. Higher dosages of Eplerenone are not recommended because they have no greater effect on blood pressure than 100 mg and are associated with an increased risk of hyperkalemia [see Clinical Studies].

Recommended Monitoring

Measure serum potassium before initiating eplerenone therapy, within the first week, and at one month after the start of treatment or dose adjustment. Assess serum potassium periodically thereafter.

Check serum potassium and serum creatinine within 3-7 days of a patient initating a moderate CYP3A inhibitor ACE inhibitors, angiotensin-II blockers or non-steroidal-anti-inflammatories.

Dose Modification for Use with Moderate CYP3A Inhibitors

In heart failure after recent myocardial infarction patients receiving a moderate CYP3A inhibitor (e.g., erythromycin, saquinavir, verapamil, and fluconazole), do not exceed 25 mg once daily. In patients with hypertension receiving a moderate CYP3A inhibitor, initiate at 25 mg once daily. For inadequate blood pressure response, dosing may be increased to a maximum of 25 mg twice daily [see Drug Interactions].

Method Of Administration

Epleron 25 dan 50 film-coated tablet for oral use

CONTRAINDICATIONS

For All Patients

Eplerenone is contraindicated in all patients with:

- serum potassium > 5.5 mEq/L at initiation
- creatinine clearance ≤ 30 mL/min,
- concomitant administration of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir) [see Drug Interactions, Clinical Pharmacology]
- hypersensitivity to the active substance or to any of the excipients listed in section
- patients with severe hepatic insufficiency (Child-Pugh Class C)

- the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with eplerenone

For Patients Treated for Hypertension

Eplerenone is contraindicated for the treatment of hypertension in patients with:

- type 2 diabetes with microalbuminuria.
- serum creatinine > 2.0 mg/dL in males or > 1.8 mg/dL in females,
- creatinine clearance < 50 mL/min, or
- concomitant administration of potassium supplements or potassium-sparing diuretics (e.g., amiloride, spironolactone, or triamterene [see Warning and Precautions, Adverse Reaction, Drug Interactions and Clinical Pharmacology].

WARNINGS AND PRECAUTIONS

Hyperkalemia

The risk of hyperkalemia is higher in patients with impaired renal function, proteinuria, diabetes and those concomitantly treated with ACEs, ARBs, NSAIDs and moderate CYP3A inhibitors. Minimize the risk of hyperkalemia with proper patient selection and monitoring [see Dosage and Administration, Contraindications, Adverse Reactions, and Drug Interactions]. Monitor patients for the development of hyperkalemia until the effect of Eplerenone is established. Patients who develop hyperkalemia (5.5 – 5.9 mEq/L) may continue Eplerenone therapy with proper dose adjustment. Dose reduction decreases potassium levels. Patients on moderate CYP3A inhibitors that cannot be avoided should have their dose of Eplerenone reduced [see Drug Interactions].

ADVERSE REACTIONS

Adverse events reported are those occurring in clinical studies that are suspected relationship to treatment and in excess of placebo, or are serious and significantly in excess of placebo, or have been observed during post marketing surveillance. Adverse events are listed by body system and absolute frequency. Frequencies are defined as common (more than 1/100 to less than 1/10) or uncommon (more than 1/1000 to less than 1/100).

Blood and Lymphatic System Disorders

Uncommon: eosinophilia

Cardiac Disorders

Common: left ventricular failure, atrial fibrillation

Uncommon: tachycardia

Endocrine Disorders

Uncommon: hypothyroidism

Gastrointestinal Disorders

Common: diarrhoea, nausea, constipation, vomiting

Uncommon: flatulence

General Disorders and Administration Site Conditions

Common: asthenia

Uncommon: malaise

Hepatobiliary Disorders

Uncommon: cholecystitis

Infections and Infestations

Uncommon: pyelonephritis, infection, pharyngitis

Investigations
Common: blood urea increased, blood creatinine increased
Uncommon: epidermal growth factor receptor decreased, blood glucose increased
Metabolism and Nutrition Disorders
Common: hyperkalaemia, hypercholesterolaemia
Uncommon: hypertriglyceridaemia, dehydration, hyponatraemia
Musculoskeletal and Connective Tissue Disorders
Common: muscle spasms, back pain
Uncommon: musculoskeletal pain
Nervous System Disorders
Common: dizziness, syncope, headache
Uncommon: hypoaesthesia
Psychiatric Disorders
Common: insomnia
Renal and Urinary Disorders
Common: renal impairment
Reproductive System and Breast Disorders
Uncommon: gynaecomastia
Respiratory, Thoracic and Mediastinal Disorders
Common: cough
Skin and Subcutaneous Tissue Disorders
Common: rash, pruritus
Uncommon: angioedema, hyperhidrosis
Vascular Disorders
Common: hypotension
Uncommon: arterial thrombosis limb, orthostatic hypotension

Reporting of Adverse Drug Reactions (ADRs)
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Telepon: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR
Reporting can also be done through our **Pharmacovigilance Center** at :
Email : pharmacovigilance@fahrenheit.co.id, pv@omegaresearch.id;
Telepon : +62-21-3905831

DRUG INTERACTIONS
Pharmacodynamic interaction
Potassium-sparing diuretics and potassium supplements

Due to increased risk of hyperkalaemia, eplerenone should not be administered to patients receiving other potassium-sparing diuretics and potassium supplements. Potassium-sparing diuretics may also potentiate the effect of antihypertensive agents and other diuretics.

ACE inhibitors, ARBs

The risk of hyperkalaemia may increase when eplerenone is used in combination with an ACE inhibitor and/or an ARB. A close monitoring of serum potassium and renal function is recommended, especially in patients at risk for impaired renal function, e.g., the elderly. The triple combination of an ACE inhibitor and an ARB with eplerenone should not be used.

Lithium

Drug interaction studies of eplerenone have not been conducted with lithium. However, lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors (see section Contraindications). Co-administration of eplerenone and lithium should be avoided. If this combination appears necessary, lithium plasma concentrations should be monitored.

Cyclosporin, tacrolimus

Cyclosporin and tacrolimus may lead to impaired renal function and increase the risk of hyperkalaemia. The concomitant use of eplerenone and cyclosporin or tacrolimus should be avoided. If needed, close monitoring of serum potassium and renal function are recommended when cyclosporine and tacrolimus are to be administered during treatment with eplerenone.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Acute renal failure may occur in at risk patients (elderly, dehydrated subjects, using diuretics, with impaired renal function) due to decreased glomerular filtration (inhibition of vasodilatory prostaglandins due to non-steroidal anti-inflammatory drugs). These effects are generally reversible. Furthermore, there may be a reduction of the antihypertensive effect. Hydrate the patient and monitor renal function at the beginning of treatment and regularly during the combination.

Trimethoprim

The concomitant administration of trimethoprim with eplerenone increases the risk of hyperkalaemia. Monitoring of serum potassium and renal function should be made, particularly in patients with renal impairment and in the elderly.

Alpha-1-blockers (e.g., prazosin, alfuzosine)

When alpha-1-blockers are combined with eplerenone, there is the potential for increased hypotensive effect and/or postural hypotension. Clinical monitoring for postural hypotension is recommended during alpha-1-blocker co-administration.

Tricyclic anti-depressants, neuroleptics, amifostine, baclofen

Co-administration of these drugs with eplerenone may potentially increase antihypertensive effects and risk of postural hypotension.

Glucocorticoids, tetracosactide

Co-administration of these drugs with eplerenone may potentially decrease antihypertensive effects (sodium and fluid retention).

Pharmacokinetic interactions

In vitro studies indicate that eplerenone is not an inhibitor of CYP1A2, CYP2C19, CYP2C9, CYP2D6 or CYP3A4 isozymes. Eplerenone is not a substrate or an inhibitor of P-Glycoprotein.

Digoxin

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 therapeutic range.

Warfarin

No clinically significant pharmacokinetic interactions have been observed with warfarin. Caution is warranted when warfarin is dosed near the upper limit of therapeutic range.

CYP3A4 substrates

Results of pharmacokinetic studies with CYP3A4 probe-substrates, i.e. midazolam and cisapride, showed no significant pharmacokinetic interactions when these drugs were co-administered with eplerenone.

CYP3A4 inhibitors

- Strong CYP3A4 inhibitors: Significant pharmacokinetic interactions may occur when eplerenone is co-administered with drugs that inhibit the CYP3A4 enzyme. A strong inhibitor of CYP3A4 (ketoconazole 200 mg BID) led to a 441% increase in AUC of eplerenone. The concomitant use of eplerenone with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazadone is contraindicated.
- Mild to moderate CYP3A4 inhibitors: Co-administration with erythromycin, saquinavir, amiodarone, diltiazem, verapamil, or fluconazole has led to significant pharmacokinetic interactions with rank order increases in AUC ranging from 98% to 187%. Eplerenone dosing should therefore not exceed 25 mg daily when mild to moderate inhibitors of CYP3A4 are co-administered with eplerenone.

CYP3A4 inducers

Co-administration of St John's wort (a strong CYP3A4 inducer) with eplerenone caused a 30% decrease in eplerenone AUC. A more pronounced decrease in eplerenone AUC may occur with stronger CYP3A4 inducers such as rifampicin. Due to the risk of decreased eplerenone efficacy, the concomitant use of strong CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St John's wort) with eplerenone is not recommended.

Antacids

Based on the results of a pharmacokinetic clinical study, no significant interaction is expected when antacids are co-administered with eplerenone.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness and syncope have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk summary

The available data form published case reports on Eplerenone use during pregnancy are insufficient to establish a drug-associated risk of major birth defects, miscarriage, adverse maternal or fetal outcomes.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknow.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk.

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension shoul be carefully monitored and managed accordingly.

Pregnant women with heart failure are at increased risk for preterm birth. Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Clinical classification of heart disease may worsen with pregnancy and lead to maternal death. Closely monitor pregnant patients for destabilization of their heart failure.

Lactation

Risk Summary

There are no human data available on whether Eplerenone is present in human milk, or has effects on breastfed infants or on milk production. Eplerenone was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Females and Males of Reproductive Potential

Infertility

The use of Eplerenone may compromise male fertility

Geriatric Use

Heart Failure Post-Myocardial Infarction

No differences in overall incidence of adverse events were observed between elderly and younger patients. However, due to age-related decreases in creatinine clearance, the incidence of laboratory-documented hyperkalemia was increased in patients 65 and older.

Hypertension

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, however due to age-related decreases in creatine clearance, the risk of hyperkalemia may be increased.

OVERDOSAGE

No cases of human overdosage with eplerenone have been reported. The most likely manifestation of human overdosage would be anticipated to be hypotension 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.

PATIENT COUNSELING INFORMATION

Advise patients receiving Eplerenone:

- Not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician [see Warnings and Precautions].
- To call their physician if they experience dizziness, diarrhea, vomiting, rapid or irregular heartbeat, lower extremity edema, or difficulty breathing [see Warnings and Precautions].

LIST OF EXCIPIENTS OF EPLERON® 25 AND 50 FILM COATED TABLET

Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Povidone, Magnesium Stearate, Talc, Coating Agent (Polyvinyl Alcohol, Titanium Dioxide, Talc, Macrogol, Lecithin (Soy)), Chocolate Brown V18013/2, FD&C Yellow No.6 Lake, Purified Water.

STORAGE
Store below at 30°C

PRESENTATION
Epleron® 25 Film-Coated Tablet :
Box, 3 blister @ 10 film coated tablet, Reg No. DKL2431551517A1
Epleron® 50 Film-Coated Tablet :
Box, 3 blister @ 10 film coated tablet, Reg No. DKL2431551517B1

DRUG CLASSIFICATION
Prescription Drug

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:
PT. PRATAPA NIRMALA
Tangerang – Indonesia

INFORMASI PRODUK UNTUK PASIEN
Epleron®
TABLET SALUT SELAPUT

Bacalah semua selebaran ini dengan seksama sebelum Anda mulai minum obat ini karena mengandung informasi penting untuk Anda.

- Simpan lembar informasi ini. Anda mungkin perlu membacanya kembali
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Ini dapat membahayakan mereka, bahkan jika tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mendapatkan efek samping, bicarakan dengan dokter atau apoteker Anda. Termasuk kemungkinan efek samping yang tidak tercantum dalam selebaran ini. Lihat bagian 4.

Isi dalam lembar informasi ini :

1. Apa itu **Epleron®** dan apa gunanya
2. Apa yang perlu Anda ketahui sebelum menggunakan **Epleron®**
3. Bagaimana **Epleron®** diberikan
4. Kemungkinan efek samping
5. Bagaimana cara menyimpan **Epleron®**
6. Informasi lebih lanjut

1. APA ITU EPLERON® DAN APA GUNANYA

Epleron® termasuk dalam kelompok obat yang dikenal sebagai agen penghambat aldosteron selektif. Agen penghambat ini menghambat aksi aldosteron, zat yang diproduksi di dalam tubuh, yang mengontrol tekanan darah dan fungsi jantung Anda. Tingkat aldosteron yang tinggi dapat menyebabkan perubahan dalam tubuh Anda yang menyebabkan gagal jantung.
Epleron® diindikasikan untuk :

- Pengobatan gagal jantung simptomatik, sebagai tambahan terapi standar termasuk beta-blocker, pada pasien stabil dengan disfungsi ventrikel kiri (LVEF ≤ 40%) dan bukti klinis gagal jantung setelah infark miokard.
- Pengobatan hipertensi ringan sampai sedang, untuk menurunkan tekanan darah.
  Epleron® dapat digunakan sendiri namun biasanya dikombinasikan dengan obat antihipertensi lainnya.

2. APA YANG PERLU ANDA KETAHUI SEBELUM MENGGUNAKAN EPLERON®

Jangan menggunakan **Epleron®** :

- Apabila Anda alergi terhadap **Epleron** atau salah satu bahan lain dari obat ini (tercantum di bagian 6).
- Apabila Anda memiliki kadar kalium yang tinggi dalam darah Anda (hiperkalemia)
- Apabila Anda sedang mengonsumsi kelompok obat yang membantu Anda mengeluarkan cairan tubuh yang berlebihan (diuretik hemat kalium)
- Apabila Anda memiliki penyakit ginjal yang parah
- Apabila Anda memiliki penyakit hati yang parah

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- Apabila Anda sedang mengonsumsi obat-obatan yang digunakan untuk mengobati infeksi jamur (ketoconazole atau itraconazole)
- Apabila Anda menggunakan obat antivirus untuk mengobati HIV (nelfinavir atau ritonavir)
- Apabila Anda sedang mengonsumsi antibiotik yang digunakan untuk mengobati infeksi bakteri (clarithromycin atau telithromycin)
- Apabila Anda mengonsumsi nefazodone digunakan untuk mengobati depresi.
- Apabila Anda menggunakan obat yang digunakan untuk mengobati kondisi jantung atau hipertensi tertentu (disebut penghambat enzim pengubah angiotensin (ACE) dan penghambat reseptor angiotensin (ARB)) secara bersamaan.

Peringatan dan Perhatian

Bicaralah dengan dokter atau apoteker atau perawat Anda sebelum menggunakan **Epleron®** :

- Apabila Anda memiliki penyakit ginjal atau hati (lihat juga "Jangan menggunakan **Epleron®**")
- Apabila Anda menggunakan lithium (biasanya diberikan untuk gangguan manik-depresif, juga disebut gangguan bipolar)
- Apabila Anda menggunakan tacrolimus atau cyclosporin (digunakan untuk mengobati kondisi kulit seperti psoriasis atau eksim, dan untuk mencegah penolakan setelah transplantasi organ).

Epleron® dan Obat-obatan lainnya

Beri tahu dokter atau apoteker Anda jika Anda sedang mengonsumsi, baru saja mengonsumsi atau mungkin sedang mengonsumsi obat lain.

Anda tidak boleh mengonsumsi tablet **Epleron** bersama dengan obat-obatan berikut :

- Itrakonazol atau ketokonazol (digunakan untuk mengobati infeksi jamur), ritonavir, nelfinavir (obat antivirus untuk mengobati HIV), clarithromycin, telithromycin (digunakan untuk mengobati infeksi bakteri) atau nefazodone (digunakan untuk mengobati depresi) karena obat ini mengurangi eliminasi **Epleron** pada tubuh, sehingga memperpanjang efeknya pada tubuh.
- Diuretik hemat kalium (obat yang membantu Anda mengeluarkan kelebihan cairan tubuh) dan suplemen kalium (tablet garam) karena obat ini meningkatkan risiko kadar kalium tinggi dalam darah Anda.
- Penghambat enzim pengubah angiotensin (ACE) dan penghambat reseptor angiotensin (ARB) bersama-sama (yang digunakan untuk mengobati tekanan darah tinggi, penyakit jantung atau kondisi ginjal tertentu) karena obat ini dapat meningkatkan risiko kadar kalium tinggi dalam darah Anda.
- Litium (biasanya diberikan untuk gangguan manik-depresif, juga disebut gangguan bipolar). Penggunaan lithium bersama dengan diuretik dan inhibitor ACE (digunakan untuk mengobati tekanan darah tinggi dan penyakit jantung) telah terbukti menyebabkan tingkat lithium dalam darah menjadi terlalu tinggi, yang dapat menyebabkan efek samping: kehilangan nafsu makan; gangguan penglihatan; kelelahan; kelemahan otot; otot berkedut.
- Cyclosporin atau tacrolimus (digunakan untuk mengobati kondisi kulit seperti psoriasis atau eksim, dan untuk mencegah penolakan setelah transplantasi organ). Obat ini dapat

menyebabkan masalah ginjal dan karena itu meningkatkan risiko kadar kalium tinggi dalam darah Anda.

- Obat anti-inflamasi nonsteroid (NSAID - obat penghilang rasa sakit tertentu seperti ibuprofen, digunakan untuk menghilangkan rasa sakit, kekakuan dan peradangan). Obat-obatan ini dapat menyebabkan masalah ginjal dan karena itu meningkatkan risiko kadar kalium tinggi dalam darah Anda.
- Trimethoprim (digunakan untuk mengobati infeksi bakteri) dapat meningkatkan risiko kadar kalium tinggi dalam darah Anda.
- Alpha I bloker, seperti prazosin atau alfuzosin (digunakan untuk mengobati tekanan darah tinggi dan kondisi prostat tertentu) dapat menyebabkan penurunan tekanan darah dan pusing saat berdiri.
- Antidepresan tricyclic seperti amitryptyline atau amoxapine (untuk pengobatan depresi), antipsikotik (juga dikenal sebagai neuroleptik) seperti chlorpromazine atau haloperidol (untuk pengobatan gangguan kejiwaan), amifostine (digunakan selama kemoterapi kanker) dan baclofen (digunakan untuk mengobati otot kekejangan). Obat-obatan ini dapat menyebabkan penurunan tekanan darah dan pusing saat berdiri.
- Glucocortiroids, seperti hydrocortisone atau prednisolone (digunakan untuk mengobati peradangan dan kondisi kulit tertentu) dan tetracosactide (terutama digunakan untuk mendiagnosis dan mengobati gangguan pada korteks adrenal) dapat mengurangi efek penurunan tekanan darah dari **Epleron**.
- Digoxin (digunakan dalam pengobatan kondisi jantung). Kadar digoxin dalam darah dapat meningkat bila dikonsumsi bersamaan dengan **Epleron**.
- Warfarin (obat anti pembekuan darah): Perhatian diperlukan saat mengonsumsi warfarin karena kadar warfarin yang tinggi dalam darah dapat menyebabkan perubahan efek **Epleron** pada tubuh.
- Erythromycin (digunakan untuk mengobati infeksi bakteri), saquinavir (obat antivirus untuk mengobati HIV), fluconazole (digunakan untuk mengobati infeksi jamur), amiodarone, diltiazem dan verapamil (untuk pengobatan masalah jantung dan tekanan darah tinggi) mengurangi kerusakan **Epleron** sehingga memperpanjang efek **Epleron** pada tubuh.
- St John's Wort (produk obat herbal), rifampicin (digunakan untuk mengobati infeksi bakteri), carbamazepin, phenytoin, dan phenobarbital (digunakan, antara lain, untuk mengobati epilepsi) dapat meningkatkan pemecahan **Epleron** dan dengan demikian mengurangi efeknya.

Epleron® dengan makanan dan minuman
Epleron® dapat diminum dengan atau tanpa makanan.

Kehamilan dan menyusui
Jika Anda sedang hamil atau menyusui, berpikir Anda mungkin hamil atau berencana untuk memiliki bayi, mintalah nasihat dokter atau apoteker Anda sebelum minum obat ini. Efek **Epleron®** belum dievaluasi selama kehamilan pada manusia.
Tidak diketahui apakah **Epleron®** diekskresikan dalam ASI manusia. Keputusan harus dibuat dengan dokter Anda, apakah akan menghentikan menyusui atau menghentikan obat.

Mengemudi dan menggunakan mesin
Anda mungkin merasa pusing setelah meminum **Epleron®**. Jika ini terjadi, jangan mengemudi atau mengoperasikan mesin.

3. BAGAIMANA EPLERON® DIGUNAKAN
Selalu minum obat ini persis seperti yang dikatakan dokter atau apoteker Anda. Tanyakan kepada dokter atau apoteker Anda jika Anda tidak yakin.

- Untuk indikasi gagal jantung simptomatik dan baru mengalami infark miokard (serangan jantung) :
  Pengobatan awal dengan **Epleron** dimulai dari dosis 25 mg satu kali sehari dan dapat ditingkatkan hingga dosis yang dianjurkan sebesar 50 mg , sebaiknya dikonsumsi dalam waktu 4 minggu sesuai kondisi masing-masing pasien.
- Untuk Hipertensi :
  Direkomendasikan untuk memulai pengobatan dengan satu tablet **Epleron** 50 mg satu kali sehari selama 4 minggu. Jika tidak ada respon tekanan darah yang memadai terhadap dosis **Epleron** 50 mg satu kali sehari, maka dosis dapat ditingkatkan menjadi 50 mg dua kali sehari. Dosis **Epleron** yang lebih tinggi (lebih dari 100 mg per hari) tidak direkomendasikan karena tidak memberikan efek yang lebih besar untuk menurunkan tekanan darah dan dapat terjadi peningkatan risiko hiperkalemia.

Kadar kalium darah harus diukur sebelum memulai terapi **Epleron®**, dalam minggu pertama dan satu bulan setelah dimulainya pengobatan atau setelah perubahan dosis. Dosis dapat disesuaikan oleh dokter Anda, tergantung pada kadar kalium dalam darah Anda.

Jika Anda mengonsumsi lebih banyak Epleron® dari yang seharusnya
Jika Anda mengonsumsi **Epleron®** lebih banyak dari yang seharusnya, segera beri tahu dokter atau apoteker Anda. Jika Anda telah minum terlalu banyak obat Anda, gejala yang paling mungkin adalah tekanan darah rendah (dinyatakan sebagai perasaan ringan di kepala Anda, pusing, penglihatan kabur, kelemahan, kehilangan kesadaran akut) atau hiperkalemia, kadar kalium yang tinggi dalam darah (diekspresikan oleh kram otot, diare, mual, pusing atau sakit kepala).

Jika Anda lupa meminum Epleron®
Jika hampir waktunya untuk tablet berikutnya, lewati tablet yang seharusnya Anda minum dan ambil tablet berikutnya saat jatuh tempo.
Jika tidak, minumlah tablet segera setelah Anda ingat, asalkan ada lebih dari 12 jam sebelum Anda harus meminum tablet berikutnya. Kemudian kembali minum obat seperti biasa.
Jangan mengambil dosis ganda untuk mengganti tablet yang terlupakan.

Jika Anda berhenti minum Epleron®
Penting untuk tetap menggunakan **Epleron®** seperti yang ditentukan kecuali dokter Anda memberi tahu Anda untuk menghentikan perawatan Anda.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

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4. KEMUNGKINAN EFEK SAMPING

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya. Efek samping yang dilaporkan :

Efek samping yang umum (dapat mempengaruhi lebih dari 1 dari 100 orang hingga kurang dari 1 dari 10 orang) :

- Gagal ventrikel kiri (kondisi ketika ventrikel kiri jantung tidak dapat memompa darah dengan baik ke seluruh tubuh, yang menyebabkan tubuh kekurangan oksigen dan darah (sesak napas))
- Fibrilasi atrium (gangguan irama jantung yang ditandai dengan denyut jantung tidak beraturan dan cepat).
- Diare, mual, sembelit, muntah
- Asthenia (kondisi fisik tubuh melemah dan ditandai dengan lemas pada bagian tubuh tertentu atau seluruh tubuh, sakit kepala, nyeri dada dan sesak napas serta sulit bicara)
- Peningkatan kadar urea dalam darah
- Peningkatan kadar kreatinin darah
- Peningkatan kadar kalium dalam darah Anda (gejalanya meliputi kram otot, diare, mual, pusing, atau sakit kepala)
- Peningkatan jumlah kolesterol dalam darah Anda
- Kejang otot (kram otot), Sakit punggung
- Pusing, Sinkop (Pingsan), Sakit kepala
- Insomnia (sulit tidur)
- Gangguan ginjal
- Batuk
- Ruam, pruritus (gatal)
- Hipotensi (kondisi ketika tekanan darah jauh lebih rendah dari yang seharusnya)

Efek samping yang jarang terjadi (dapat mempengaruhi lebih dari 1 dari 1000 orang hingga kurang dari 1 dari 100 orang) :

- Eosinofilia (peningkatan sel darah putih tertentu)
- Takikardia (kondisi jantung yang berdetak melebihi 100 kali per menit)
- Hipotiroidisme (gangguan kesehatan yang terjadi karena kurangnya produksi hormon tiroid oleh kelenjar tiroid)
- Perut kembung
- Malaise (perasaan lelah, tidak nyaman dan kurang enak badan)
- Kolesistitis (peradangan pada kantong empedu)
- Pielonefritis (infeksi pada saluran kemih bagian atas, khususnya pada bagian parenkim dan pelvis ginjal)
- Infeksi
- Faringitis (peradangan pada faring atau tenggorokan)
- Reseptor faktor pertumbuhan epidermis menurun, peningkatan glukosa dalam darah.
- Hipertrigliseredemia (kondisi medis ketika kadar trigliserida dalam darah melebihi batas normal)
- Dehidrasi (kondisi ketika tubuh kekurangan cairan)

- Hiponatraemia (gangguan elektrolit yang disebabkan oleh rendahnya kadar natrium di dalam darah)
- Nyeri muskuloskeletal
- Hipoestesia (penurunan sensitivitas terhadap stimulasi atau defisit modalitas sensorik (berkurangnya rasa sentuhan))
- Ginekomastia (kondisi pembesaran jaringan payudara pada pria)
- Angioedema (pembengkakan pada jaringan submukosa, subkutan dan dermis. Umumnya menyerang bibir, mata, dan wajah, tetapi dapat pula menyerang tubuh lain seperti saluran pencernaan, genital, dan saluran pernafasan termasuk laring)
- Hiperhidrosis (kondisi ketika produksi keringat berlebihan)
- Tungkai thrombosis arteri (kondisi ketika terjadi gumpalan darah di pembuluh darah arteri di kaki).
- Hipotensi ortostatik (kondisi tekanan darah rendah yang terjadi akibat perubahan posisi tubuh, misalnya dari berbaring lalu bangkit berdiri)

Pelaporan efek samping
Jika mengalami efek samping apa pun, sampaikan kepada dokter atau apoteker termasuk jika mengalami efek samping yang mungkin terjadi yang tidak tercantum pada leaflet ini. Dengan melaporkan efek samping yang terjadi, anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini. Laporkan setiap efek samping yang dicurigai merugikan pada kami di:
Email: pharmacovigilance@fahrenheit.co.id, pv@omegaresearch.id; Telepon : +62-21-3905831

5. BAGAIMANA CARA MENYIMPAN EPLERON®

Simpan pada suhu di bawah 30°C.
Jangan menggunakan obat ini setelah tanggal kadaluwarsa yang tertera pada kemasan dus dan blister.
Jangan membuang obat-obatan melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. INFORMASI LEBIH LANJUT

Apa kandungan **Epleron® 25 dan 50 Tablet Salut Selaput**
Bahan aktif : **Epleron**.
Bahan tambahan : Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Povidone, Magnesium Stearate, Talc, Bahan Penyalut (Polyvinyl Alcohol, Titanium Dioxide, Talc, Macrogol, Lecithin (Soy), Chocolate Brown V18013/2, FD&C Yellow No.6 Lake, Purified Water.

Seperti apa rupa **Epleron® 25 dan 50 Tablet Salut Selaput** dan isi kemasannya

Epleron® 25 Tablet Salut Selaput : tablet salut selaput berwarna coklat dengan logo  dan polos.

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Epleron® 50 Tablet Salut Selaput : tablet salut selaput berwarna coklat dengan logo dan polos.

Kemasan :
Epleron® 25 Tablet Salut Selaput :
Dus, 3 blister @ 10 tablet salut selaput, Reg No. DKL2431551517A1
Epleron® 50 Tablet Salut Selaput :
Dus, 3 blister @ 10 tablet salut selaput, Reg No. DKL2431551517B1

HARUS DENGAN RESEP DOKTER

Diproduksi Oleh
PT. PRATAPA NIRMALA
Tangerang – Indonesia

FAHRENHEIT

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