STORAGE
As directed by the physician
Store below 30°C in a dry place,
protect from light.
Keep all medicines out of the reach of children

خوراک : ڈاکٹر کی ہدایت کے مطابق۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر
روشنی سے بچا کر خشک جگہ پر رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔

PRESENTATION
EPLER 50 mg, Pack of Alu Alu 1x10's

Manufactured by:
Platinum Pharmaceuticals (Pvt) Ltd.
A-20,North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

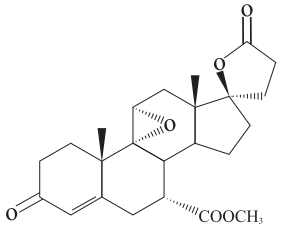
QAR No. AW11-0002

Epler Tablet 50 mg
(Eplerenone)

ایپلر ٹیبلیٹ ۵۰ ملی گرام
(ایپلرینون)

COMPOSITION
Each film coated tablet contains:
Eplerenone (Platinum Spec.) ..... 50 mg
Product complies Platinum Spec.

DESCRIPTION
Eplerenone is a blocker of aldosterone binding at the mineralocorticoid receptor. Eplerenone is chemically described as Pregn-4-ene-7,21-dicarboxylic acid, 9,11- epoxy-17-hydroxy-3-oxo-,γ-lactone, methyl-ester,(7α,11α,17α). Its emeprical formula is $C_{24}H_{30}O_6$ and it has a molecular weight of 414.50. Structural formula of eplerenone is represented below:



PHARMACOLOGICAL ACTIONS
Pharmacodynamic properties:
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 non- epithelial (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 recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Pharmacokinetic properties:
Absorption: Mean peak plasma concentrations of eplerenone are reached approximately 1.5 hours following oral administration. Absorption is not affected by food.

Distribution: The apparent volume of distribution at steady state ranged from 43 to 90 L. Eplerenone does not preferentially bind to red blood cells.

Metabolism: Eplerenone metabolism is primarily mediated via CYP3A4. No active metabolites

of eplerenone have been identified in human plasma.
Excretion: 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 4 to 6 hours.

INDICATIONS AND USAGE

Congestive Heart Failure Post-Myocardial Infarction
To improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction.

Hypertension
Eplerenone may be used alone or in combination with other antihypertensive agents

DOSAGE AND ADMINISTRATION

Congestive Heart Failure Post-Myocardial Infarction
The recommended dose is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily, preferably within 4 weeks as tolerated by the patient. Drug may be administered with or without food. Serum potassium should be measured before initiating therapy, within the first week and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter.

Hypertension
Eplerenone may be used alone or in combination with other antihypertensive agents. The recommended starting dose is 50 mg administered once daily. The full therapeutic effect is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50 mg once daily, the dosage of eplerenone (Epler) should be increased to 50 mg twice daily. Higher dosages are not recommended either because they have no greater effect on blood pressure than 100 mg or because they are associated with an increased risk of hyperkalemia.

Recommended Monitoring
Serum potassium should be measured before initiating eplerenone (Epler) therapy, within the first week, and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter. Patient characteristics and serum potassium levels may indicate that additional monitoring is appropriate.

CONTRAINDICATIONS

The drug is contraindicated in all patients with:
- serum potassium >5.5 mEq/L at initiation,
- creatinine clearance ≤30 ml/min, or
- concomitant use with the following potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir)

The drug is also contraindicated for the treatment of hypertension in patients with the following:
- 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.

ADVERSE EFFECTS

Headache, dizziness, angina pectoris/myocardial infarction, increased GGT, diarrhea, abdominal pain, hypercholesterolemia and hypertriglyceridemia

WARNINGS AND SPECIAL PRECAUTIONS

Pregnancy
Pregnancy Category B:
There are no adequate and well-controlled studies in pregnant women. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects
Embryo-fetal development studies were conducted with doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits (exposures up to 32 and 31 times the human AUC for the 100 mg/day therapeutic dose, respectively). No teratogenic effects were seen in rats or rabbits, although decreased body weight in maternal rabbits and increased rabbit fetal resorptions and post-implantation loss were observed at the highest administered dosage. Because animal reproduction studies are not always predictive of human response, eplerenone (Epler) should be used during pregnancy only if clearly needed.

Nursing mothers
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.

Hepatic impairment
No adjustment of the starting dose is recommended for the elderly or for patients with mild-to, moderate hepatic impairment.

DRUG INTERACTIONS

Inhibitors of CYP3A4: Eplerenone metabolism is predominantly mediated via CYP3A4. Ketoconazole a potent inhibitor of the CYP3A4 pathway, showed a 1.7-fold increase in Cmax of eplerenone. The drug should not be used with drugs described as strong inhibitors of CYP3A4. Administration of eplerenone with other CYP3A4 inhibitors (e.g., erythromycin, verapamil, saquinavir, fluconazole) resulted in increases in Cmax of eplerenone ranging from 1.4- to 1.6-fold.

Lithium: Lithium, toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Serum lithium levels should be monitored frequently when eplerenone is administered concomitantly with lithium.

Non-steroidal Anti-Inflammatory Drugs (NSAIDs): A drug interaction study of eplerenone with an NSAID has not been conducted. The administration of other potassium-sparing antihypertensive 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 ere used concomitantly, patients should be observed to determine whether the desired effect on blood pressure is obtained.

OVERDOSAGE

No cases of human over dosage with eplerenone have been reported. The most likely manifestation of human over dosage 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 initialed.