Eplerenone
Core Safety Profile

4.3. Contraindications

- Hypersensitivity to eplerenone or any of the excipients (see section 6.1).
- Patients with serum potassium level > 5.0 mmol/L at initiation
- Patients with severe renal insufficiency (eGFR <30 mL per minute per 1.73 m2)
- Patients with severe hepatic insufficiency (Child-Pugh Class C)
- Patients receiving potassium-sparing diuretics, potassium-supplements or strong inhibitors of CYP 3A4 (eg itraconazole, ketoconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazodone) (see section 4.5).
- The combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with eplerenone

4.4. Special warnings and precautions for use

Hyperkalaemia: Consistent with its mechanism of action, hyperkalaemia may occur with eplerenone. Serum potassium levels should be monitored in all patients at initiation of treatment and with a change in dosage. Thereafter, periodic monitoring is recommended especially in patients at risk for the development of hyperkalaemia, such as (elderly) patients, patients with renal insufficiency (see section 4.2) and patients with diabetes. The use of potassium supplements after initiation of eplerenone therapy is not recommended, due to an increased risk of hyperkalaemia. Dose reduction of eplerenone has been shown to decrease serum potassium levels. In one study, the addition of hydrochlorothiazide to eplerenone therapy has been shown to offset increases in serum potassium.

The risk of hyperkalaemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB). The combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with eplerenone should not be used (see sections 4.3 and 4.5).

Impaired renal function: Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria. The risk of hyperkalaemia increases with decreasing renal function. While the data from EPHESUS in patients with type 2 diabetes and microalbuminuria is limited, an increased occurrence of hyperkalaemia was observed in this small number of patients. Therefore, these patients should be treated with caution. Eplerenone is not removed by haemodialysis.

Impaired hepatic function: No elevations of serum potassium above 5.5 mmol/L were observed in patients with mild to moderate hepatic impairment (Child Pugh class A and B). Electrolyte levels should be monitored in patients with mild to moderate hepatic impairment. The use of eplerenone in patients with severe hepatic impairment has not been evaluated and its use is therefore contraindicated (see sections 4.2 and 4.3).

CYP3A4 inducers: Coadministration of eplerenone with strong CYP3A4 inducers is not recommended (see section 4.5).

Lithium, cyclosporin, tacromilus should be avoided during treatment with eplerenone (see section 4.5).

Lactose: The tablets contain lactose and should not be administered in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5. Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Potassium-sparing diuretics and potassium supplements: Due to increased risk of hyperkalaemia, eplerenone should not be administered to patients receiving other potassiumsparing diuretics and

potassium supplements (see section 4.3). Potassium-sparing diuretics may also potentiate the effect of anti-hypertensive agents and other diuretics.

ACE inhibitors, angiotensin receptor blockers (ARB): The risk of hyperkalaemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (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 angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with eplerenone should not be used (see sections 4.3 and 4.4).

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 4.4). Co-administration of eplerenone and lithium should be avoided. If this combination appears necessary, lithium plasma concentrations should be monitored (see section 4.4).

Cyclosporin, tacrolimus: Cyclosporin and tacromilus 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 (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs): Treatment with NSAIDs may lead to acute renal failure by acting directly on glomerular filtration, especially in at-risk patients (elderly and/or dehydrated patients). Patients receiving eplerenone and NSAIDs should be adequately hydrated and be monitored for renal function prior to initiating treatment.

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 coadministration.

Tricyclic anti-depressants, neuroleptics, amifostine, baclofene: 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
Digoxin: While a statistically significant 16% increase in AUC0-24 was observed with digoxin 200 mcg and eplerenone 100 mg once daily in a pharmacokinetic study in healthy volunteers, this increase was not accompanied by clinical evidence of digoxin toxicity. 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.

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

CYP3A4 inhibitors:

- Strong CYP3A4 inhibitors: Significant pharmacokinetic interactions may occur when eplerenone is coadministered 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 (see

section 4.3). The concomitant use of eplerenone with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazadone, is contra-indicated (see section 4.3).

- Mild to moderate CYP3A4 inhibitors: Co-administration with erythromycin, saquinavir, amiodarone, diltiazem, verapamil, and fluconazole have led to significant pharmacokinetic interactions with rank order increases in AUC ranging from 98% to 187%. Eplerenone dosing should therefore not exceed 25 mg when mild to moderate inhibitors of CYP3A4 are coadministered with eplerenone (see sections 4.2).

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 (see section 4.4).

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

4.6. Pregnancy and lactation

Pregnancy: There are no adequate data on the use of eplerenone in pregnant women. Animal studies did not indicate direct or indirect adverse effects with respect to pregnancy, embryofoetal development, parturition and postnatal development (see section 5.3). Caution should be exercised prescribing eplerenone to pregnant women.

Lactation: It is unknown if eplerenone is excreted in human breast milk after oral administration. However, preclinical data show that eplerenone and/or metabolites are present in rat breast milk and that rat pups exposed by this route developed normally. Because of the unknown potential for adverse effects on the breast fed infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7. Effects on ability to drive and use machines

No studies on the effect of eplerenone on the ability to drive or use machines have been performed. Eplerenone does not cause drowsiness or impairment of cognitive function but when driving vehicles or operating machines it should be taken into account that dizziness may occur during treatment.

4.8. Undesirable effects

In two studies (Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS] and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure [EMPHASIS-HF]), the overall incidence of adverse events reported with eplerenone was similar to placebo. The most frequent adverse event reported in the EMPHASIS-HF study was hyperkalaemia with an incidence rate of 8.7% and 4% for eplerenone and placebo respectively.

Adverse events reported below are those with 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 > 1/100, < 1/10; uncommon > 1/1000, < 1/100.

System Organ Class	**Frequency**	**Undesirable effects**
Infections and infestations	Common	infection
	Uncommon	Pyelonephritis, pharyngitis
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Endocrine disorders	Uncommon	Hypothyroidism
Metabolism and nutrition disorders	Common	Hyperkalaemia (see section 4.3 and 4.4)
	Uncommon	Hyponatraemia, dehydration, hypercholesterolaemia, hypertriglyceridaemia

Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Common	Dizziness, Syncope
	Uncommon	Headache, Hypoaesthesia
Cardiac disorders	Common	Myocardial infarction,
	Uncommon	Left ventricular failure, atrial fibrillation, tachycardia
Vascular disorders	Common	Hypotension
	Uncommon	Arterial thrombosis limb, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Common	Diarrhoea, nausea, constipation
	Uncommon	Vomiting, flatulence
Skin and subcutaneous tissue disorders	Common	Rash, Pruritus
	Uncommon	Hyperhidrosis
	Not known	Angioedema
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, musculoskeletal pain
	Uncommon	Back pain
Renal and urinary disorders	Common	Renal impairement (see section 4.3 and 4.4)
Hepatobiliary disorders	Uncommon	Cholecystitis
Reproductive system and breast disorders	Uncommon	Gynaecomastia
General disorders and administration site conditions	Uncommon	Asthenia, malaise
Investigations	Common	Blood urea increased
	Uncommon	Blood creatinine increase, epidermal growth factor receptor decreased, blood glucose increased

In EPHESUS, there were numerically more cases of stroke in the very elderly group (> 75 years old). There was however no statistical significant difference between the occurrence of stroke in the eplerenone (30) vs placebo (22) groups. In EMPHASIS-HF, the number of cases of stroke in the very elderly (≥ 75 years old) was 9 in the eplerenone group and 8 in the placebo group.

4.9. Overdose

No cases of adverse events associated with overdose of eplerenone in humans have been reported.

The most likely manifestation of human overdosage would be anticipated to be hypotension and/or hyperkalaemia. If symptomatic hypotension should occur, supportive treatment should be initiated. If hyperkalaemia develops, standard treatment should be initiated.

Eplerenone cannot be removed by haemodialysis. Eplerenone has been shown to bind extensively to charcoal.