Summary of Product Characteristics

1. Name of drug product

EPLEINTA- 50mg Tablets

2. Qualitative and quantitative compositions

Each film coated tablet contains:
Eplerenone Ph.Eur. 50 mg

Excipients with known effect:
Lactose monohydrate

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated tablet.

Yellow diamond shape biconvex film-coated tablets, debossed with "E2" on one side and plain on other side.

4. Clinical particulars:

4.1. Therapeutics indications:

Eplerenone is indicated:

- in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction.
- in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with New York Heart Association (NYHA) class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30%).

4.2. Posology and method of administration: Posology

For the individual adjustment of dose, the strengths of 25 mg and 50 mg are available. The maximum dose regimen is 50 mg daily.
For post-myocardial infarction heart failure patients:
The recommended maintenance dose of eplerenone is 50 mg once daily (OD). Treatment should be initiated at 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 1). Eplerenone therapy should usually be started within 3-14 days after an acute myocardial infarction.
For patients with NYHA class II (chronic) heart failure:
For chronic heart failure NYHA class II patients, 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 1).
Patients with a serum potassium of > 5.0 mmol/L should not be started on eplerenone. Serum potassium should be measured before initiating eplerenone therapy, within the first week and at one month after the start of treatment or dose adjustment. Serum potassium should be

assessed as needed periodically thereafter.
After initiation, the dose should be adjusted based on the serum potassium level as shown in Table 1.

Table 1: Dose adjustment table after initiation

Serum potassium (mmol/L)	**Action**	**Dose adjustment**
< 5.0	Increase	25 mg EOD* to 25 mg OD 25 mg OD to 50 mg OD
5.0 – 5.4	Maintain	No dose adjustment
5.5 – 5.9	Decrease	50 mg OD to 25 mg OD 25 mg OD to 25 mg EOD* 25 mg EOD* to withhold
≥ 6.0	Withhold	N/A

* EOD: Every Other Day

Following withholding eplerenone due to serum potassium ≥ 6.0 mmol/L, eplerenone can be re-started at a dose of 25 mg every other day when potassium levels have fallen below 5.0 mmol/L.

Paediatric population

The safety and efficacy of eplerenone in children and adolescents have not been established. *Elderly*

No initial dose adjustment is required in the elderly. Due to an age-related decline in renal function, the risk of hyperkalaemia 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.

Renal impairment

No initial dose adjustment is required in patients with mild renal impairment. Periodic monitoring of serum potassium with doses adjusted according to Table 1 is recommended.

Patients with moderate renal impairment (CrCl 30-60 ml/min) should be started at 25 mg every other day, and dose should be adjusted based on the potassium level (see Table 1). Periodic monitoring of serum potassium is recommended.

There is no experience in patients with CrCl <50 ml/min with post MI heart failure. The use of eplerenone in these patients should be done cautiously.

Doses above 25 mg daily have not been studied in patients with CrCl <50 ml/min. Patients with severe renal impairment (CrCl <30 ml/min) are contraindicated.

Eplerenone is not dialysable.

Hepatic impairment

No initial dosage adjustment is necessary for patients with mild-to-moderate hepatic impairment. Due to an increased systemic exposure to eplerenone in patients with mild-to-moderate hepatic impairment, frequent and regular monitoring of serum potassium is recommended in these patients, especially when elderly.

Concomitant treatment

In case of concomitant treatment with mild to moderate CYP3A4 inhibitors, e.g. amiodarone, diltiazem and verapamil, a starting dose of

25 mg OD may be initiated. Dosing should not exceed 25 mg OD.

Method of administration
Eplerenone may be administered with or without food. The tablets should be swallowed whole with plenty of water.

4.3. Contra-indications:

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with serum potassium level > 5.0 mmol/L at initiation
- Patients with severe renal insufficiency (eGFR < 30 mL/min/1.73 m2)
- Patients with severe hepatic insufficiency (Child-Pugh Class C)
- Patients receiving potassium-sparing diuretics, potassium-supplements or strong inhibitors of CYP3A4 (eg itraconazole, ketoconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazodone)
- The combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with Eplerenone.

4.4. Special warning 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 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.
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 Eplerenone Post-acute Myocardial Infarction Heart failure Efficacy and Survival Study (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.
CYP3A4 inducers
Co-administration of eplerenone with strong CYP3A4 inducers is not recommended. *Lithium, cyclosporin, tacrolimus* should be avoided during treatment with eplerenone. *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 drugs, other forms of interactions:
Pharmacodynamic interactions
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 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.
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. 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)
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, alfuzosin)
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 contra-indicated.
- 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 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.

4.6. Use in 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. Caution should be exercised prescribing eplerenone to pregnant women.

Breastfeeding

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.

Fertility

There are no human data available on fertility.

4.7. Effects on ability to drive and operate machine:

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.

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:

Very common (≥ 1/ 10) Common (≥ 1/ 100 to < 1/ 10),

Uncommon (≥ 1/ 1,000 to < 1/ 100). Rare (≥ 1/ 10,000 to <1/ 1,000) Very rare (<1/ 10,000)

Not known (cannot be estimated from the available data).

Infections and infestations

Uncommon: pyelonephritis, infection, pharyngitis **Blood and lymphatic system disorders** *Uncommon*: eosinophilia

Endocrine disorders

Uncommon: hypothyroidism

Metabolism and nutrition disorders

Common: hyperkalaemia, hypercholesterolaemia

Uncommon: hyponatraemia, dehydration, hypertriglyceridaemia

Psychiatric disorders

Common: insomnia

Nervous system disorders
Common: dizziness, syncope, headache
Uncommon: hypoaesthesia
Cardiac disorders
Common: left ventricular failure, atrial fibrillation
Uncommon: tachycardia **Vascular disorders** *Common*: hypotension
Uncommon: arterial thrombosis limb, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders *Common:* cough
Gastrointestinal disorders
Common: diarrhoea, nausea, constipation, vomiting
Uncommon: flatulence **Hepatobiliary disorders** *Uncommon*: cholecystitis
Skin and subcutaneous tissue disorders
Common: rash, pruritus
Uncommon: hyperhidrosis, angioedema **Musculoskeletal and connective tissue disorders** *Common:* muscle spasm, back pain
Uncommon: musculoskeletal pain
Renal and urinary disorders *Common*: renal impairment
Reproductive system and breast disorders *Uncommon:* gynaecomastia
General disorders and administration site conditions *Common:* asthenia
Uncommon: malaise
Investigations
Common: blood urea increased, blood creatinine increased
Uncommon: 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.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9. Overdoses:
No cases of adverse events associated with overdose of eplerenone in humans have been reported. The most likely manifestation of human overdose would be anticipated to be hypotension or hyperkalaemia. Eplerenone cannot be removed by haemodialysis. Eplerenone has been shown to bind extensively to charcoal. If symptomatic hypotension should occur, supportive treatment should be initiated. If hyperkalaemia develops, standard treatment should be initiated.

5. Pharmacological properties:
5.1. Pharmaco-dynamic properties:
Pharmacotherapeutic group: aldosterone antagonists, ATC code: C03DA04

Mechanism of action

Eplerenone has relative selectivity in binding to recombinant human mineralocorticoid receptors compared to its binding to recombinant human glucocorticoid, progesterone and androgen receptors. Eplerenone prevents the binding of aldosterone, a key hormone in the renin-angiotensin-aldosterone-system (RAAS), which is involved in the regulation of blood pressure and the pathophysiology of cardiovascular disease.

Pharmacodynamic effects

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.

Paediatric population:

Eplerenone has not been studied in paediatric subjects with heart failure. Any (long term) effect on hormonal status in paediatric subjects has not been studied.

5.2. Pharmaco-kinetic properties:

Absorption

The absolute bioavailability of eplerenone is 69% following administration of a 100mg oral tablet. Maximum plasma concentrations are reached after about 2 hours. Both peak plasma levels (Cmax) and area under the curve (AUC) are dose proportional for doses of 10 to 100 mg and less than proportional at doses above 100 mg. Steady state is reached within 2 days. Absorption is not affected by food.

Distribution

The plasma protein binding of eplerenone is about 50 % and is primarily bound to alpha 1-acid glycoproteins. The apparent volume of distribution at steady state is estimated at 50 (±7) L. Eplerenone does not preferentially bind to red blood cells.

Biotransformation

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

Elimination

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

Special Populations

Age, Gender, and Race

The pharmacokinetics of eplerenone at a dose of 100 mg once daily have 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 Cmax (22 %) and AUC (45 %) compared with younger subjects (18 to 45 years). At steady state, Cmax was 19 % lower and AUC was 26 % lower in blacks.

Paediatric population

A population pharmacokinetic model for eplerenone concentrations from two studies in 51 paediatric hypertensive patients of ages 4-16 years identified that patient body weight had a statistically significant effect on eplerenone volume of distribution but not on its clearance. Eplerenone volume of distribution and peak exposure in a heavier paediatric subjects are predicted to be similar to that in an adult of similar body weight; in a lighter 45 kg patient, the volume of distribution is about 40% lower and the peak exposure is predicted to be higher than typical adults. Eplerenone treatment was initiated at 25 mg once daily in paediatric patients and increased to 25 mg twice daily after 2 weeks and eventually to 50 mg twice daily, if clinically indicated. At these doses, the highest observed eplerenone concentrations in paediatric subjects were not substantially higher than those in adults initiated at 50 mg once daily.

Renal Insufficiency

The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of renal insufficiency and in patients undergoing haemodialysis. 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 haemodialysis. No correlation was observed between plasma clearance of eplerenone and creatinine clearance. Eplerenone is not removed by haemodialysis.

Hepatic Insufficiency

The pharmacokinetics of eplerenone 400 mg have 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. Since the use of eplerenone has not been investigated in patients with severe hepatic impairment, eplerenone is contraindicated in this patients' group.

Heart Failure

The pharmacokinetics of eplerenone 50 mg were evaluated in patients with heart failure (NYHA classification II-IV). Compared with healthy subjects matched according to age, weight and gender, steady state AUC and Cmax in heart failure patients were 38 % and 30 % higher, respectively. Consistent with these results, a population pharmacokinetic analysis of eplerenone based on a subset of patients from EPHESUS indicates that clearance of eplerenone in patients with heart failure was similar to that in healthy elderly subjects

5.3. Pre-clinical safety data:

Preclinical studies on safety pharmacology, genotoxicity, carcinogenic potential and reproductive toxicity revealed no special hazard for humans.

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

6. Pharmaceutical particulars:

6.1. List of excipients:

Core:

Lactose monohydrate
Microcrystalline cellulose (Avicel PH101) Hypromellose
Croscarmellose sodium
Microcrystalline cellulose (Avicel PH102) Purified Talc
Magnesium stearate

Coating:

Opadry 13B520013 Yellow

6.2. Incompatibilities:

Not applicable

6.3. Shelf-life:

36 Months

6.4. Special precaution for storage:

Do not store above 30°C.
Keep out of the reach and sight of children.

6.5. Nature and contents of container:

10 Tablets are packed in Alu-White Opaque PVC blister. Such 3 blisters are packed in printed carton with package insert

7. Marketing authorization holder

Intas Pharmaceuticals Limited Corporate House,
Near Sola Bridge,
S.G. Highway,
Thaltej, Ahmedabad-380054
India.

Manufacturer:

INTAS PHARMACEUTICALS LTD.
Matoda-382 210,
Dist. Ahmedabad,
India.

8. Marketing Authorization Number

H2024/CTD7989/16302

9. Date of first authorization/renewal of the authorization

31/07/2024

10. Date of revision of the text

24/08/2026