HPRA An tÚdarás Rialála Táirgí Sláinte Health Products Regulatory Authority

INSPRA

50 Milligram Film Coated Tablet

Pfizer Healthcare Ireland PA0822/020/002

Main Information

Trade Name INSPRA
Active Substances EPLERENONE
Strength 50 Milligram
Dosage Form Film Coated Tablet
Licence Holder Pfizer Healthcare Ireland
Licence Number PA0822/020/002

Group Information

ATC Code C03DA04 Aldosterone antagonists

Status

Authorised/Withdrawn Authorised
Licence Issued 20/08/2004
Supply Status Supply through pharmacies only
Dispensing Status Product subject to prescription which may be renewed (B)
Marketing Status Marketed
Promotion Status Promotion to Healthcare Professionals only
Conditions of Licence

Documents

Summary of Product Characteristics PDF Version
Package Leaflet PDF Version
Public Assessment Report No document available
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Summary of Product Characteristics

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

INSPRA 50 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of eplerenone.

Excipients with known effect
Each 50 mg tablet contains 71.4 mg of lactose monohydrate (see section 4.4).

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

50 mg tablet: yellow tablet with stylized “Pfizer” on one side of tablet, “NSR” over “50”on the other side of tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Eplerenone is indicated:

- in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular (CV) mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction (MI).
- in addition to standard optimal therapy, to reduce the risk of CV mortality and morbidity in adult patients with New York Heart Association (NYHA) class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30%) (see section 5.1).

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- MI 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 MI.
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 and section 4.4).

Patients with a serum potassium of > 5.0 mmol/L should not be started on eplerenone (see section 4.3).

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. Currently available data are described in section 5.1 and 5.2.

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 (see section 4.4).

Renal impairment
No initial dose adjustment is required in patients with mild renal impairment. Periodic monitoring of serum potassium with dose adjustment 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 (see section 4.4).

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. Use in patients with severe renal impairment (CrCl <30 mL/min) is contraindicated (see section 4.3).
Eplerenone is not dialysable.

Hepatic impairment
No initial dose 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 (see section 4.4).

Concomitant treatment
In case of concomitant treatment with mild to moderate CYP3A4 inhibitors, e.g. amiodarone, diltiazem and verapamil, the dose of 25 mg OD may be initiated. Dosing should not exceed 25 mg OD (see section 4.5).

Eplerenone may be administered with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in 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 m^2)
- Patients with severe hepatic insufficiency (Child-Pugh Class C)
- Patients receiving potassium-sparing diuretics or strong inhibitors of CYP 3A4 (e.g., 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 ACE inhibitor and/or an ARB. The combination of an ACE inhibitor and an 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 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 (see sections 4.2 and 4.3).

CYP3A4 inducers
Co-administration of eplerenone with strong CYP3A4 inducers is not recommended (see section 4.5).

Lithium, cyclosporin, tacrolimus 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 potassium-sparing 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, 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 (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 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 (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 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 (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, 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 (see section 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 Fertility, 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.

Breast-feeding

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 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 (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).

Table 2: ADR Frequency in Eplerenone Placebo Controlled Studies

MedDRA system organ class	**Adverse reaction**
Infections and infestations	
Uncommon	pyelonephritis, infection, pharyngitis
Blood and lymphatic system disorders	
Uncommon	eosinophilia
Endocrine disorders	
Uncommon	hypothyroidism
Metabolism and nutrition disorders	
Common	hyperkalaemia (see sections 4.3 and 4.4), hypercholesterolaemia
Uncommon	hyponatraemia, dehydration, hypertriglyceridaemia
Psychiatric disorders	
Common	insomnia
Nervous system disorders	
Common	syncope , dizziness, 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
Skin and subcutaneous tissue disorders	
Common	rash, pruritus
Uncommon	angioedema, hyperhidrosis
Musculoskeletal and connective tissue disorders	
Common	muscle spasms, back pain
Uncommon	musculoskeletal pain
Renal and urinary disorders	
Common	renal impairment (see sections 4.4 and 4.5)
Hepatobiliary disorders	
Uncommon	cholecystitis
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
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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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 Pharmacodynamic 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 CV 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.

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

Eplerenone was studied in the EPHESUS. EPHESUS was a double-blind, placebo-controlled study, of 3 year duration, in 6632 subjects with acute MI, left ventricular dysfunction (as measured by left ventricular ejection fraction [LVEF] ≤40%), and clinical signs of heart failure. Within 3 to 14 days (median 7 days) after an acute MI, subjects received eplerenone or placebo in addition to standard therapies at an initial dose of 25 mg once daily and titrated to the target dose of 50 mg once daily after 4 weeks if serum potassium was < 5.0 mmol/L. During the study subjects received standard care including acetylsalicylic acid (92%), ACE inhibitors (90%), beta-blockers (83%), nitrates (72%), loop diuretics (66%), or HMG CoA reductase inhibitors (60%).

In EPHESUS, the co-primary endpoints were all-cause mortality and the combined endpoint of CV death or CV hospitalisation; 14.4 % of subjects assigned to eplerenone and 16.7 % of subjects assigned to placebo died (all causes), while 26.7 % of subjects assigned to eplerenone and 30.0 % assigned to placebo met the combined endpoint of CV death or hospitalisation. Thus, in EPHESUS, eplerenone reduced the risk of death from any cause by 15% (RR 0.85; 95% CI, 0.75-0.96; p= 0.008) compared to placebo, primarily by reducing CV mortality. The risk of CV death or CV hospitalisation was reduced by 13% with eplerenone (RR 0.87; 95% CI, 0.79-0.95; p=0.002). The absolute risk reductions for the endpoints all cause mortality and CV mortality/hospitalisation were 2.3% and 3.3%, respectively. Clinical efficacy was primarily demonstrated when eplerenone therapy was initiated in subjects aged < 75 years old.

The benefits of therapy in those subjects over the age of 75 are unclear. NYHA functional classification improved or remained stable for a statistically significant greater proportion of subjects receiving eplerenone compared to placebo. The incidence of hyperkalaemia was 3.4 % in the eplerenone group vs. 2.0 % in the placebo group ($p < 0.001$). The incidence of hypokalaemia was 0.5 % in the eplerenone group vs. 1.5 % in the placebo group ($p < 0.001$).

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.

In the EMPHASIS-HF trial the effect of eplerenone when added to standard therapy was investigated on clinical outcomes in subjects with systolic heart failure and mild symptoms (NYHA functional class II).

Subjects were included if they were at least 55 years old, had a LVEF ≤ 30% or LVEF ≤ 35% in addition to QRS duration of > 130 msec, and were either hospitalized for CV reasons 6 months prior to inclusion or had a plasma level of B-type natriuretic peptide (BNP) of at least 250 pg/mL or a plasma level of N-terminal pro-BNP of at least 500 pg/mL in men (750 pg/mL in women). Eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily if the serum potassium level was < 5.0 mmol/L. Alternatively, if the estimated glomerular filtration rate (GFR) was 30-49 mL/min/1.73 m^2, eplerenone was started at 25 mg on alternate days, and increased to 25 mg once daily.

In total, 2737 subjects were randomized (double-blind) to treatment with eplerenone or placebo including baseline therapy of diuretics (85%), ACE inhibitors (78%), angiotensin II receptor blockers (19%), beta-blockers (87%), anti thrombotic drugs (88%), lipid lowering agents (63%), and digitalis glycosides (27%). The mean LVEF was ~26% and the mean QRS duration was ~122 msec. Most of the subjects (83.4%) were previously hospitalized for CV reasons within 6 months of randomization, with around 50% of them due to heart failure. Around 20% of the subjects had implantable defibrillators or cardiac resynchronization therapy.

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

The secondary endpoint of all cause mortality was met by 171 (12.5%) subjects in the eplerenone group and 213 (15.5%) subjects in the placebo group (RR 0.76; 95% CI, 0.62-0.93; $p = 0.008$). Death from CV causes was reported in 147 (10.8%) subjects in the eplerenone group and 185 (13.5%) subjects in the placebo group (RR 0.76; 95% CI, 0.61-0.94; $p = 0.01$).

During the study, hyperkalaemia (serum potassium level > 5.5 mmol/L) was reported in 158 (11.8%) subjects in the eplerenone group and 96 (7.2%) subjects in the placebo group ($p < 0.001$). Hypokalaemia, defined as serum potassium levels < 4.0 mmol/L, was statistically lower with eplerenone when compared to placebo (38.9% for eplerenone compared to 48.4% for placebo, $p<0.0001$).

Paediatric population
Eplerenone has not been studied in pediatric subjects with heart failure.

In a 10 week study of paediatric subjects with hypertension (age range 4 to 16 years, n=304), eplerenone, at doses (from 25 mg up to 100 mg per day) that produced exposure similar to that in adults, did not lower blood pressure effectively. In this study and in a 1-year paediatric safety study in 149 subjects (age range 5 to 17 years), the safety profile was similar to that of adults. Eplerenone has not been studied in hypertensive subjects less than 4 years old because the study in older paediatric subjects showed a lack of efficacy (see section 4.2).

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

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of eplerenone is 69% following administration of a 100 mg oral tablet.
Maximum plasma concentrations are reached after approximately 1.5 to 2 hours. Both peak plasma levels (Cmax) and area under the curve (AUC) are dose proportional for doses of 10 mg 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 to be 42-90 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 6 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 C_{max} (22%) and AUC (45%) compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19% lower and AUC was 26% lower in blacks (see section 4.2).

Paediatric population
A population pharmacokinetic model for eplerenone concentrations from two studies in 51 paediatric hypertensive subjects of ages 4 to 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 patient 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 (see section 4.4.).

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 (see section 4.2). Since the use of eplerenone has not been investigated in patients with severe hepatic impairment, eplerenone is contraindicated in this patient group (see section 4.3).

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 Preclinical safety data

Preclinical studies of 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

Tablet core:
Lactose monohydrate
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Hypromellose (E464)
Sodium laurilsulfate
Talc (E553b)
Magnesium stearate (E470b)

Tablet coating:
Opadry yellow:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Polysorbate 80 (E433)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Opaque PVC/Al blisters containing 10, 20, 28, 30, 50, 90, 100 or 200 tablets
Opaque PVC/Al perforated unit dose blisters containing 10 x 1, 20 x 1, 30 x 1, 50 x 1, 90 x 1, 100 x 1 or 200 x 1 (10 packs of 20 x 1) tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland

9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/020/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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