Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Inspra 25 mg Film Coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of eplerenone

Excipient: Each 25 mg tablet contains 35.7 mg lactose monohydrate (see Section 4.4.)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet

Product imported from Poland:
Yellow tablet with stylized ‘Pfizer’ on one side of tablet, ‘NSR’ over ‘25’ 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 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 NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30%) (see section 5.1).

4.2 Posology and method of administration

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 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.

Children and adolescents
There are no data to recommend the use of eplerenone in the paediatric population, and therefore, use in this age group is not recommended.

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 is recommended (see section 4.4) and doses adjusted according to Table 1

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.

Patients with severe renal impairment (CrCl <30 ml/min) are contraindicated (see section 4.3).
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 (see section 4.4).

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 (see section 4.5).

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

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 eplerenon

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 section 4.3).

CYP3A4 inducers: Coadministration 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, 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). Coadministration 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 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 co-administered 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 coadministered 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.

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 surve*illance*. Adverse events are listed by body system and absolute frequency. Frequencies are defined as: common > 1/100, < 1/10; uncommon > 1/1000, < 1/100.*

Infections and infestations
Common: infection
Uncommon: pyelonephritis

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, hypoaesthhesia

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 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
Uncommon: asthenia, malaise

Investigations
Common: Blood urea increased
Uncommon: blood creatinine increased, 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 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

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.

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 Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). EPHESUS was a double-blind, placebo-controlled study, of 3 year duration, in 6632 patients with acute myocardial infarction (MI), left ventricular dysfunction (as measured by left ventricular ejection fraction [LVEF] ≤40%), and clinical signs of heart failure. Within 3-14 days (median 7 days) after an acute MI, patients received eplerenone or placebo in addition to standard therapies at an initial dose 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 patients received standard care including acetylsalicylic acid (92%), ACE inhibitors (90%), ß-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 patients assigned to eplerenone and 16.7 % of patients assigned to placebo died (all causes), while 26.7 % of patients 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 cardiovascular (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 patients aged < 75 years old. The benefits of therapy in those patients over the age of 75 are unclear. NYHA functional classification improved or remained stable for a statistically significantly greater proportion of patients 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 (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) the effect of eplerenone when added to standard therapy was investigated on clinical outcomes in patients with systolic heart failure and mild symptoms (NYHA functional class II).

Patients were included if they were at least 55 years old, had a left ventricular ejection fraction (LVEF) ≤30% or LVEF ≤35% in addition to QRS duration of > 130 msec, and were either hospitalized for cardiovascular (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 GFR was 30-49 ml/min/1.73 m2, eplerenone was started at 25 mg on alternate days, and increased to 25 mg once daily.

In total, 2737 patients were randomized (double-blind) to the 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 patients (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 patients had implantable defibrillators or cardiac resynchronization therapy.

The primary endpoint, death from cardiovascular causes or hospitalization for heart failure occurred in 249 patients (18.3%) in the eplerenone group and 356 patients (25.9%) 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 patients (12.5%) in the eplerenone group and 213 patients (15.5%) 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%) patients in the eplerenone group and 185 (13.5%) patients 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 patients (11.8%) in the eplerenone group and 96 patients (7.2%) 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).

5.2 Pharmacokinetic properties

Absorption and Distribution:
The absolute bioavailability of eplerenone is unknown. 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.

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.

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 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 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.)*

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 patients' 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 on safety pharmacology, genotoxicity, carcinogenic potential and toxicity to reproduction 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
Croscarmellose sodium
Hypromellose
Sodium laurilsulfate
Talc
Magnesium stearate

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer packaging of the product on the market in the country of origin.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blisters in a cardboard carton containing 30 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Clear Pharmacy,
157-173 Roden Street,
Belfast,
BT12 5QA,
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1596/48/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th April 2011

10 DATE OF REVISION OF THE TEXT

October 2012