ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SERENONE™ 25 mg, film-coated tablet

SERENONE™ 50 mg, film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eplerenone .....25 mg

For one film-coated tablet.

Excipient with known effect: one tablet contains 34.5 mg lactose monohydrate (see section 4.4). For the full list of excipients, see section 6.1.

Eplerenone .....50 mg

For one film-coated tablet.

Excipient with known effect: one tablet contains 69 mg lactose monohydrate (see section 4.4). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

SERENONE™ 25 mg: Yellow, round, biconvex tablet, diameter 6.0 mm.

SERENONE™ 50 mg: Yellow, round, biconvex tablet, diameter 7.5 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SERENONE™ is indicated:

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

4.2. Posology and method of administration

Posology

It is possible to use 25 mg and 50 mg dosages for individual adjustment of the posology. The maximum dosage is of 50 mg daily.

For patients with heart failure after myocardial infarction

The recommended maintenance dose of eplerenone is 50 mg once daily. The treatment should be started at 25 mg dose once daily, with an increase of the dosage to the target daily dose of 50 mg once daily preferably within four weeks, taking into account serum potassium levels (see table 1). Eplerenone treatment should usually be started within 3-14 days after severe myocardial infarction.

For patients with class II chronic heart failure according to NYHA classification

For patients with NYHA class II chronic heart failure, treatment should be started at a dose of 25 mg once daily and may be increased up to the dose of 50 mg/day, preferably within 4 weeks, after verifying blood potassium (see Table 1 and section 4.4).

Eplerenone treatment should not be initiated in patients with serum potassium > 5.0 mmol/L (see section 4.3).

Serum potassium should be measured before initiating eplerenone treatment, during the first week and then one month after the start of treatment or dose adjustment. Serum potassium should be assessed as needed periodically thereafter.

After the start of treatment, the dosage should be adjusted as a function of the serum potassium as indicated in table 1.

Table 1: Dosage adjustment after start of treatment

Serum potassium (mmol/L)	**Action**	**Dosage adjustment**
< 5.0	Increase	25 mg every other day then 25 mg once a day. 25 mg once a day to 50 mg once a day.
5.0 – 5.4	Maintain	No dosage adjustment
5.5 – 5.9	Decrease	50 mg once a day to 25 mg once a day. 25 mg once a day to 25 mg every other day. 25 mg every other day up to treatment interruption.
≥ 6.0	Interruption	Not applicable.

Following eplerenone treatment interruption due to serum potassium ≥ 6.0 mmol/L, the treatment may be resumed at a dosage of 25 mg every other day as soon as serum potassium levels fall 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 sections 5.1 and 5.2.

Elderly

No initial dosage adjustment is required in the elderly. Due to an age-related decline in renal function, the risk of hyperkalaemia is increased in this population. This risk may also be higher when there is also a co-morbidity associated with increased systemic exposure, in particular mild to moderate hepatic impairment. Regular monitoring of serum potassium is recommended (see section 4.4).

Renal impairment

No initial dosage adjustment is required in patients with mild renal impairment. Regular monitoring of serum potassium with dosage adjustment according to table 1 is recommended.

In patients with moderate renal impairment (CrCl 30-60 mL/min) treatment should be initiated at 25 mg every other day, and dose should be adjusted based on the potassium level (see Table 1). Regular monitoring of serum potassium is recommended (see section 4.4).

There is no data in patients with CrCl < 50 mL/min with heart failure after myocardial infarction. The use of eplerenone in these patients should be performed with caution. Doses higher than 25 mg per day 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 dosage adjustment is required in patients with mild to moderate hepatic impairment. However, due to an increased systemic exposure to eplerenone in these patients, frequent and regular monitoring of blood potassium is recommended, especially in the elderly (see section 4.4).

Concomitant treatment

In case of concomitant treatment with mild to moderate CYP3A4 inhibitors, for example amiodarone, diltiazem and verapamil, an initial dosage of 25 mg once a day should be used. The dosage should not exceed 25 mg once a day (see section 4.5).

Eplerenone may be taken 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 > 5.0 mmol/L at initiation of treatment;
- patients with severe renal impairment (GFR < 30 mL per minute per 1.73 m^2);
- patients with severe hepatic impairment (Child-Pugh Class C);
- patients receiving potassium-sparing diuretics, potassium supplements or potent CYP3A4 inhibitors (for example itraconazole, ketoconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazodone) (see section 4.5);
- combination with an angiotensine converting enzyme (ACE) inhibitor and an angiotensin II receptor blocker (ARB).

4.4. Special warnings and precautions for use

Hyperkalaemia

Hyperkalaemia may occur under eplerenone treatment due to its mechanism of action. Serum potassium should be monitored in all patients at initiation of treatment and at modifications of the dosage. Thereafter, regular monitoring is recommended especially for patients at risk of hyperkalaemia, such as elderly patients, patients with renal impairment (see section 4.2) and diabetic patients. The administration of potassium supplements after start of treatment with eplerenone is not recommended due to an increased risk of hyperkalaemia. A decrease in serum potassium has been observed when eplerenone dosage is reduced. A study demonstrated that the combination of hydrochlorothiazide with an eplerenone treatment counterbalanced the increase in serum potassium.

The risk of hyperkalaemia may increase when eplerenone is used combined 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).

Renal impairment

Blood potassium should be monitored regularly in patients with renal impairment, especially diabetic microalbuminuria. The risk of hyperkalaemia increases with decreasing renal function. Even though the data of patients with type II diabetes and microalbuminuria are limited in the study EPHESUS (Eplerenone Post-acute Myocardial Infarction Heart failure Efficacy and Survival Study), an increased incidence of hyperkalaemia was observed in these patients. Therefore, they should be treated with caution. Eplerenone is not eliminated by haemodialysis.

Hepatic impairment

No increase in blood potassium above 5.5 mmol/L was observed in patients with mild to moderate hepatic impairment (Child-Pugh A and B). Electrolyte concentrations should be monitored in patients presenting mild to moderate hepatic impairment. The use of eplerenone was not evaluated in patients with severe hepatic impairment and therefore it is contraindicated (see section 4.2 and 4.3).

CYP3A4 inducers

The administration of eplerenone with potent CYP3A4 inducers is not recommended (see section 4.5).

Lithium, ciclosporin, tacrolimus should be avoided during eplerenone treatment (see section 4.5).

Lactose

This medicine contains lactose. Patients with galactose intolerance, total Lapp lactase deficiency or glucose and galactose malabsorption syndrome (rare hereditary diseases) should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. it is essentially “sodium-free”.

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

Pharmacodynamic interactions

+ Potassium-sparing diuretics and potassium supplements

Due to the increased risk of hyperkalaemia, eplerenone should not be administered to patients receiving other potassium-sparing diuretics or potassium supplements (see section 4.3). Potassium-sparing diuretics may also potentiate the effect of anti-hypertensive agents and other diuretics.

+ ACE inhibitors, ARB

The risk of hyperkalaemia may increase when eplerenone is used combined with an ACE inhibitor and/or ARB. Close monitoring of serum potassium and renal function is recommended, especially in patients at risk for renal impairment, for example elderly patients.

The triple combination of an ACE inhibitor and an ARB with eplerenone should not be used (see sections 4.3 and 4.4).

+ Lithium

No drug-interaction study has been conducted with lithium. However, lithium toxicity has been observed in patients receiving lithium, diuretics and ACE inhibitors (see section 4.4). Concomitant administration of eplerenone and lithium should be avoided. If this combination appears necessary, lithium plasma concentrations should be monitored (see section 4.4).

+ Ciclosporin, tacrolimus

Ciclosporin and tacrolimus may cause renal impairment and increase the risk of hyperkalaemia. Concomitant use of eplerenone and ciclosporin or tacrolimus should be avoided. When ciclosporin and tacrolimus must be administered with eplerenone (see section 4.4), close control of serum potassium and renal function is recommended.

+ Non-steroid anti-inflammatory drugs (NSAIDs)

Acute renal impairment may occur in at-risk patients (elderly, dehydrated patients, using diuretics, with impaired renal function) due to decreased glomerular filtration (inhibition of vasodilator prostaglandins due to non-steroidal anti-inflammatory drugs). These effects are generally reversible. Furthermore, there may be a reduction of the antihypertensive effect. Hydrate the patients and monitor renal function at start of treatment and regularly during the combination (see sections 4.2 and 4.4).

+ Trimethoprim

Concomitant administration of trimethoprim and eplerenone increases the risk of hyperkalaemia. Monitoring of serum potassium and renal function should be conducted, especially in patients with renal impairment and in the elderly.

+ Alpha-1-blockers (for example prazosin, alfuzosin)

In case of combination of alpha-1-blockers and eplerenone, there is a potential risk of increase in the hypotensive effect and/or orthostatic hypotension. Clinical monitoring of orthostatic hypotension is recommended for concomitant administration with alpha-1-blockers.

+ Tricyclic anti-depressants, neuroleptics, amifostine, baclofen

There is a potential risk of increase in antihypertensive effects and orthostatic hypotension if these medicinal products are combined with eplerenone.

+ Glucocorticoids, tetracosactide

Concurrent administration of these medicinal products with eplerenone may potentially decrease the antihypertensive effects (sodium and fluid retention).

Pharmacokinetic interactions

In vitro studies have shown that eplerenone is not an inhibitor of CYP1A2, CYP2C19, CYP2C9, CYP2D6 or CYP3A4 isoenzymes. Eplerenone is not a substrate or an inhibitor of P-glycoprotein.

+ Digoxin

Systemic exposure (AUC) to digoxin increases by 16% (90% CI: 4% - 30%) in case of concomitant administration with eplerenone. Precautions for use are required if the digoxin level is close to the upper therapeutic limit.

+ Warfarin

No clinically significant pharmacokinetic interactions have been observed with warfarin. Precautions for use are required if the warfarin level is close to the upper therapeutic limit.

+ CYP3A4 substrates

Results of pharmacokinetic studies with CYP3A4 labelled substrates, midazolam and cisapride, showed no significant pharmacokinetic interactions in case of concomitant administration of these medicinal products with eplerenone.

+ CYP3A4 inhibitors

Potent CYP3A4 inhibitors: significant pharmacokinetic interactions may occur in case of combination with medicinal products that inhibit CYP3A4. A potent CYP3A4 inhibitor (ketoconazole at 200 mg two times daily) results in an increase of 441 % of the AUC of eplerenone (see section 4.3). The concomitant use of eplerenone with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin or nefazodone is contraindicated (see section 4.3).

Mild to moderate CYP3A4 inhibitors: concomitant administration with erythromycin, saquinavir, amiodarone, diltiazem, verapamil and fluconazole results in significant pharmacokinetic interactions with increases in AUC ranging from 98 % to 187 %. Eplerenone dosage should not exceed 25 mg daily when combined with mild to moderate CYP3A4 inhibitors (see section 4.2).

+ CYP3A4 inducers

Concomitant administration of St. John's wort (potent CYP3A4 inducer) and eplerenone results in a 30 % decrease in eplerenone AUC. A more pronounced decrease in eplerenone AUC may occur with more potent CYP3A4 inducers such as rifampicin. Due to the risk of reduced eplerenone efficacy, simultaneous use of potent CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort) and eplerenone is not recommended (see section 4.4).

+ Antacids

The results of a clinical kinetic study showed that no significant interaction is expected when antacids are combined with eplerenone.

4.6. Fertility, pregnancy and lactation

Pregnancy

There is insufficient data on the use of eplerenone in pregnant women. Animal studies have not revealed any direct or indirect undesirable effects on gestation, embryonic/foetal development, parturition and post-natal development (see section 5.3). However, caution is recommended when prescribing eplerenone to pregnant women.

Lactation

After oral administration, it is not known if eplerenone is excreted in milk. However, preclinical data show that eplerenone and/or its metabolites are present in rat milk and that rat pups exposed by this route developed normally. Since adverse drug reactions in case of breast-feeding are not known, a decision on whether to discontinue breast-feeding or the treatment should be made taking into consideration the importance of the treatment for the mother.

Fertility

There are no data available on fertility.

4.7. Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed. Eplerenone does not cause drowsiness or insufficiency of cognitive functions. However, the potential risk of dizziness should be taken into consideration when driving or using machines.

4.8. Undesirable effects

In two studies (EPHESUS and EMPHASIS-HF [Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure]), the overall incidence of adverse events described with eplerenone was similar to that observed with placebo.

The adverse events presented below are those for which a relationship with the treatment is suspected or for which the incidence is higher than that observed with placebo, serious adverse events for which the incidence is significantly higher than that observed with placebo or those observed during post-marketing monitoring. Adverse events are classified by system-organ and absolute frequency. The frequency is defined as follows:

- very common (≥ 1/10);
- common (≥ 1/100, < 1/10);
- uncommon (≥ 1/1,000, <1/100);
- rare (≥ 1/10,000, <1/1,000);
- very rare (<1/10,000);
- not known (cannot be estimated from the available data).

Table 2: Frequency of adverse events in placebo-controlled studies performed with eplerenone

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 of the limbs, orthostatic hypotension

MedDRA system organ class	Adverse reaction
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal disorders	
Common	diarrhoea, nausea, constipation, vomiting
Uncommon	Flatulence
Skin and subcutaneous tissue disorders	
Common	skin rash, pruritus
Uncommon	angioedema, hyperhidrosis
Musculoskeletal and systemic disorders	
Common	muscle spasms, back pain
Uncommon	musculoskeletal pain
Renal and urinary tract 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 the EPHESUS study, a higher number of cases of stroke were observed in the very elderly patient (≥ 75 years) group. However, no statistically significant difference in the occurrence of stroke was demonstrated between the eplerenone (30) and placebo (22) groups. In the EMPHASIS-HF study, the number of cases of stroke in very elderly persons (≥ 75 years) 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 the national reporting system.

4.9. Overdose

No cases of overdose have been reported with eplerenone in humans. The most likely manifestation of overdose would be hypotension or hyperkalaemia. Eplerenone cannot be eliminated by haemodialysis. Eplerenone has been shown to bind extensively to charcoal.

If symptomatic hypotension should occur, supportive treatment should be initiated. If

hyperkalaemia should occur, standard treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Aldosterone antagonist, ATC code: C03DA04.

Mechanism of action

Eplerenone shows relatively selective binding to recombinant human mineralocorticoid receptors compared to its binding to recombinant human glucocorticoid, progesterone and androgen receptors. Eplerenone prevents the binding of aldosterone, an essential hormone of the renin-angiotensin-aldosterone-system (RAAS), which is involved in the regulation of blood pressure and the pathophysiology of cardiovascular disease.

Pharmacodynamic effects

Eplerenone induced sustained increases in plasma renin and serum aldosterone, corresponding to a negative feedback inhibition of aldosterone on renin secretion. The increase in plasma renin activity and the circulating aldosterone levels do not compensate the eplerenone effects.

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

Eplerenone was evaluated in the EPHESUS study. It is a double-blind, placebo-controlled study, over 3 years, conducted in 6632 subjects with acute myocardial infarction (MI), presenting left ventricular dysfunction (with left ventricular ejection fraction [LVEF] ≤ 40%),and clinical signs of heart failure.

Within 3 to 14 days (median: 7 days) after an acute myocardial infarction, subjects received eplerenone or placebo in addition to standard treatments, at an initial dose of 25 mg once a day, with an increase of the dosage to the target dose of 50 mg once a day after four weeks if serum potassium was less than 5.0 mmol/L. During the study, the subjects received a standard treatment including acetylsalicylic acid (92%), ACE inhibitors (90%), beta-blockers (83%), nitrates (72%), loop diuretics (66%), or HMG CoA reductase inhibitors (60%).

In the EPHESUS study, the primary endpoints were all-cause mortality and a combined endpoint of cardiovascular mortality or hospitalisation; 14.4 % of subjects who received eplerenone and 16.7 % of subjects who received the placebo died (all causes),while 26.7 % of subjects who received eplerenone and 30.0 % who received placebo presented the combined endpoint of cardiovascular mortality or hospitalisation. Also, in EPHESUS, eplerenone reduced the risk of mortality from all causes by 15% (RR 0.85; 95% CI, 0.75-0.96; p= 0.008) compared to placebo, primarily by reducing cardiovascular mortality. The risk of cardiovascular mortality or cardiovascular-induced 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 all-cause mortality and cardiovascular mortality or hospitalisation endpoints were 2.3% and 3.3%, respectively. Clinical efficacy was primarily demonstrated when the subjects treated with eplerenone therapy were under 75 years old. The benefits of treatment in subjects over the age of 75 years are unclear. NYHA functional classification improved or remained stable for a significantly greater proportion of subjects receiving eplerenone compared to the placebo group. 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 effect due to eplerenone on heart rate, QRS duration or PR or QT interval was observed in 147 normal subjects for whom electrocardiography modifications were assessed during the pharmacokinetic studies.

In the EMPHASIS-HF study, the effect of eplerenone on clinical signs when added to a standard treatment was examined in subjects with moderate systolic heart failure (NYHA functional class II).

The subjects included were at least 55 years old, had a LVEF ≤ 30% or LVEF ≤ 35% in addition to QRS duration of > 130 ms, and were either hospitalised for the appearance of cardiovascular (CV)

events within 6 months prior to inclusion or had a plasma levels of B-type natriuretic peptide (BNP) of at least 250 pg/mL or plasma levels of NT-pro-BNP (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 a day and was increased after 4 weeks to 50 mg once a day if the serum potassium was < 5.0 mmol/L.

Also, if the estimated glomerular filtration rate was 30-49 mL/min/1.73 m^2, eplerenone was started at a dose of 25 mg every other day, and then increased to 25 mg once a day.

In total, 2737 subjects were randomised (double-blind) to receive either eplerenone or placebo in addition to their standard treatment with diuretics (85%), angiotensin converting enzyme inhibitors (ACE inhibitors) (78%), angiotensin II receptor blockers (19%), beta-blockers (87%), antithrombotic agents (88%), lipid-lowering agents (63%), and cardiac glycosides (27%). The mean LVEF was approximately 26% and the mean QRS duration was approximately 122 ms. Most of the subjects (83.4%) had been previously hospitalised for cardiovascular events within 6 months prior to randomisation, including approximately 50% of them due to heart failure. Approximately 20% of the subjects had implantable defibrillators or cardiac resynchronisation therapy.

The primary endpoint defined by the onset of cardiovascular death or hospitalisation for heart failure was attained 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 results of the primary endpoint was the same in all pre-defined subgroups.

The secondary endpoint defined by the onset of all-cause mortality was attained in 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). Cardiovascular death 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 > 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). The occurrence of hypokalaemia, defined as serum potassium < 4.0 mmol/L, was statistically lower with eplerenone when compared to the placebo group (38.9% for eplerenone versus 48.4% for placebo, p<0.0001).

Paediatric population

Eplerenone has not been studied in paediatric subjects with heart failure.

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

The possible (long-term) effects on hormonal status in paediatric subjects have not been studied.

5.2. Pharmacokinetic properties

Absorption

The absolute bioavailability of eplerenone is 69% following oral administration of a 100 mg tablet. Maximum plasma concentrations are attained after approximately 1.5 to 2 hours. Peak plasma levels (C_{max}) and the area under the curve (AUC) are proportional to the dose for doses ranging from 10 mg to 100 mg and less proportional at doses above 100 mg. Steady state is attained 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 is primarily metabolised by CYP3A4. No active metabolite of eplerenone has been identified in human plasma.

Elimination

Less than 5% of an eplerenone dose is recovered as the unaltered form in the urine and faeces. Following a single oral dose of radioactively labelled product, approximately 32% of the dose was excreted in the faeces and approximately 67% in the urine. The elimination half-life of eplerenone is approximately 3 to 6 hours. The apparent plasma clearance is approximately 10 L/h.

Special populations

Age, sex and ethnicity-related characteristics

The pharmacokinetic properties of eplerenone at a dosage of 100 mg once a day have been studied in the elderly (65 years and over), in men and women, and in black patients. The pharmacokinetics of eplerenone was not significantly different between men and women. At steady state, increases in C_{max} (22%) and AUC (45%) were observed in elderly subjects compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19% lower and AUC was 26% lower in black patients. (see section 4.2.)

Paediatric population

A population pharmacokinetic model for eplerenone concentrations from two studies conducted in 51 paediatric hypertensive subjects aged 4 to16 years, showed 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 expected to be similar to that in an adult of equivalent body weight; in a patient under 45 kg, the volume of distribution is approximately 40% lower and the peak exposure should be higher than in an average adult. Eplerenone treatment was initiated at 25 mg once a day in paediatric patients and then increased to 25 mg twice a day after two weeks and then to 50 mg twice a day, if clinically indicated. At these doses, the highest eplerenone concentrations observed in paediatric subjects were not substantially higher than those in adults for whom the treatment was initiated with a dose of 50 mg once a day.

Renal impairment

The pharmacokinetics of eplerenone was evaluated in patients with varying degrees of renal impairment and in patients undergoing haemodialysis. Compared with subjects in the control group, steady-state AUC and C_{max} increased by 38% and 24%, respectively, in patients with severe renal impairment and 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 eliminated by haemodialysis (see section 4.4.).

Hepatic impairment

The pharmacokinetics of eplerenone at a 400 mg dosage was studied in patients with moderate (Child- Pugh Class B) hepatic impairment and compared to that of normal subjects. Steady-state C_{max} and AUC were increased by 3.6% and 42%, respectively (see section 4.2). Since the use of eplerenone has not been studied in patients with severe hepatic impairment, eplerenone is contraindicated in this type of patients (see section 4.3).

Heart failure

The pharmacokinetics of eplerenone at a 50 mg dosage was evaluated in patients with heart failure (NYHA classification II-IV). Compared to healthy subjects matched for age, weight and sex, steady state AUC and C_{max} were 38 % and 30 % higher, respectively, in patients with heart failure. Consistent with these results, a population pharmacokinetic analysis based on a subset of patients from the EPHESUS study, showed that clearance of eplerenone in patients with heart failure was similar to that in healthy elderly subjects.

5.3. Preclinical safety data

Non-clinical data from conventional safety pharmacology, genotoxicity, carcinogenic potential and toxicity to reproduction and development studies have not revealed any specific risk for humans.

In repeated dose toxicology studies, atrophy of the prostate was observed in rats and dogs at exposure levels slightly higher than clinical exposure levels. The prostate modifications were not associated with adverse functional consequences. The clinical relevance of these results is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, magnesium stearate, sodium laurilsulfate.

Film coating: OPADRY yellow 13B82402 (hypromellose, macrogol, titanium dioxide (E171), polysorbate 80, yellow iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C

6.5. Nature and contents of container

Blisters (Alu/Alu) containing 30 tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier –France
50, rue Carnot
92284 Suresnes Cedex

Date de mise à jour du texte : Mai 2021