SUMMARY OF PRODUCT CHARACTERISTICS FOR ANGIOTENSIN CONVERTING ENZYME INHIBITORS

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Additional Notes: This guideline provides a framework for the preparation of a Summary of Product Characteristics (SPC) in accordance with Directive 65/65/EEC, for a medicinal product containing an Angiotensin Converting Enzyme Inhibitor.

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SUMMARY OF PRODUCT CHARACTERISTICS FOR ANGIOTENSIN CONVERTING ENZYME INHIBITORS

1. NAME OF THE MEDICINAL PRODUCT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The pharmaceutical formulation, the active substance and the amount per pharmaceutical formulation or the concentration should be stated.

3. PHARMACEUTICAL FORM

To be completed by the company.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The following indications have been considered and approved by at least some of the Member States on the basis of satisfactory presentation of clinical data
- Hypertension
- Heart Failure
- Left Ventricular Dysfunction After Myocardial Infarction

Each indication should be justified for each separate inhibitor and for each formulation by means of sufficient clinical data.

4.2 Posology and method of administration

For each indication a separate starting dose, usual maintenance dose and maximum dose should be given. The higher the risk for first dose hypotension, the lower the starting dose.

Dosage should be adjusted to meet the individual requirements of each patient on the basis of clinical response. In hypertensive patients if the therapeutic effect cannot be achieved in a period of at least 3 weeks on a certain dose level, the dose can be further increased. The addition of a diuretic will increase even further the hypotensive effect in these patients. In patients with heart failure a period of 1-2 weeks may be required before a further increase of the dose.

First dose hypotension may occur in high risk patients (see Warnings and precautions for use). Initiation of therapy requires, if possible, correction in salt and/or body fluids deficiencies, discontinuation of an existing diuretic therapy for two to three days before ACE inhibition and the lowest starting dose. If this is not possible, initial dose should be half of the recommended starting dose.
Patients at high risk for severe acute hypotension should be monitored medically preferably in hospital for as long as its maximal effect is expected after administration of the first dose and whenever the dose of ACE inhibitor and/or diuretic is increased. This also applies to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.

In patients with malignant hypertension or severe cardiac insufficiency initiation of therapy and dose adjustment should be performed in a hospital.

It should be indicated whether the ACE inhibitor should be administered before, during or after a meal. The dose should always be taken at about the same time of day to help increase compliance.

**Dosage in renal impairment and dialysis**

Since ACE inhibitors or their active metabolites are eliminated primarily via the kidney, dosage should be reduced or the dosage interval should be increased in patients with impaired renal function in order to avoid accumulation and the risk of concentration-related substance toxicity.

Dosage recommendations should be given based on different degrees of renal impairment, as well as for patients on dialysis.

**Dosage in elderly or in hepatic impairment**

Initial dose, maintenance daily dose and maximum daily dose should be stated.

### 4.3 Contra-indications

- Hypersensitivity to the ACE inhibitor prescribed or any other ACE inhibitor.
- History of angioneurotic oedema associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioneurotic oedema
- Pregnancy
- Lactation period.

### 4.4 Warnings and precautions for use

Hypotension ACE inhibitors may cause a profound fall in blood pressure especially after the first dose. Symptomatic hypotension is rare in uncomplicated hypertensive patients. It is more likely to occur in patients who have been volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. It has been reported mainly in patients with severe heart failure with or without associated renal insufficiency. This is more likely in patients on high doses of loop diuretics, or those with hyponatraemia or functional renal impairment. In these patients treatment should be started under very close medical supervision, preferably in hospital, with low doses and careful dose titration. If possible, diuretic treatment should be discontinued temporarily. Such considerations apply also to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.

If hypotension develops, the patient should be placed in a supine position. Volume repletion with intravenous normal saline may be required. The appearance of hypotension after the initial dose.
does not preclude subsequent careful dose titration with medicinal product after effective management.

**Patients with renovascular hypertension**  There is an increased risk of severe hypotension and renal insufficiency when patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration. Diuretic treatment should be discontinued and renal function should be monitored during the first weeks of therapy.

**Patients with renal insufficiency**  Changes in renal function may be anticipated in susceptible individuals due to the inhibition of the renin-angiotensin-aldosterone system. Therefore ACE inhibitors should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses. Close monitoring of renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. Renal failure has been reported in association with ACE inhibitors, mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. Some patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine concentrations when a diuretic is given concomitantly. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required. It is recommended that the renal function be monitored during the first weeks of therapy.

Patients who are dialysed using high-flux polyacrylonitrile membranes and treated with ACE inhibitors are likely to experience anaphylactoid reactions such as facial swelling, flushing, hypotension and dyspnoea within a few minutes of commencing haemodialysis. It is recommended to use an alternative membrane or an alternative antihypertensive medicinal product.

**Angioedema**  of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ACE inhibitors which especially occurs during the first weeks of treatment. However in rare cases severe angioedema may develop after long-term treatment with an angiotensin converting enzyme inhibitor. Treatment should promptly be discontinued and replaced by an agent belonging to another class of products.

**Angioedema** involving with the tongue, glottis or larynx may be fatal. Emergency therapy should be given including, but not necessarily limited to, immediate subcutaneous adrenaline epinephrine solution 1:1000 (0.3 to 0.5 ml) or slow intravenous adrenaline 1mg/ml (observe dilution instructions) with control of ECG and blood pressure. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

**Cough**  During treatment with an ACE inhibitor a dry and non-productive cough may occur which disappears after discontinuation.

**Patients with liver insufficiency**  Patients with liver insufficiency treated with ACE inhibitors primarily metabolised in the liver may develop markedly elevated plasma levels. Dose adaptation may be necessary, depending on the severity of the liver insufficiency and the way the ACE inhibitor is metabolised.

**Elderly**  Some elderly patients may be more responsive to an ACE inhibitor than younger patients. Administration of low initial doses and evaluation of the renal function at the beginning of the treatment is recommended.
Children  ACE inhibitors should not be administered in children unless safety and efficacy have been established.

Hyperkalemia  Hyperkalemia may occur during treatment with an ACE inhibitor, especially in the presence of renal insufficiency and/or heart failure. Potassium supplements or potassium sparing diuretics are generally not recommended, since they may lead to significant increases in plasma potassium. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Surgery/Anaesthesia  ACE inhibitors may cause hypotension or even hypotensive shock in patients undergoing major surgery or during anaesthesia through the enhancement of other hypotensive potentials. If it is not possible to withhold the ACE inhibitor volume management should be handled with care.

Aortic stenosis/Hypertrophic cardiomyopathy  ACE inhibitors should be used with caution in patients with an obstruction in the outflow tract of the left ventricle.

Neutropenia/Agranulocytosis  The risk of neutropenia appears to be dose-and type-related and is dependent on patient's clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

Proteinuria  It may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

4.5 Interaction with other medicaments and other forms of interaction

- Not recommended association

Potassium sparing diuretics or potassium supplements  ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

- Precaution for use

Diuretics  Patients on diuretics and especially those who are volume-and/or salt depleted, may experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to intake and by initiation of therapy with lower doses of the ACE inhibitor. Further increases in dosage should be made with caution.

Lithium  The concomitant administration of ACE inhibitors with lithium may reduce the excretion of lithium. Serum lithium levels should be monitored frequently.

Anaesthetic medicinal products  ACE inhibitors may enhance the hypotensive effects of certain anaesthetic medicinal products.

Narcotic drugs/Antipsychotics  Postural hypotension may occur.

Antihypertensive agents  Increase of the hypotensive effect of ACE inhibitors
Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia

- **Take into account**

**Non-Steroidal Anti-inflammatory medicinal products** The administration of a non-steroidal anti-inflammatory agent may reduce the antihypertensive effect of an ACE inhibitor. Furthermore, it has been described that NSAIDS and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function.

**Antacids** Induce decreased bioavailability of ACE inhibitors.

**Sympathomimetics** may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored to confirm that the desired effect is being obtained.

**Alcohol** enhances the hypotensive effect.

**Food** may reduce the bioavailability of the ACE inhibitors.

### 4.6 Pregnancy and lactation

Appropriate and well-controlled studies have not been done in humans. ACE inhibitors cross the placenta and can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

Foetal exposure to ACE inhibitors during the second and third trimesters has been associated with neonatal hypotension, renal failure, face or skull deformities and/or death. Maternal oligohydramnios has also been reported reflecting decreasing renal function in the foetus. Limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. Oliguria should be treated with support of blood pressure and renal perfusion.

Intrauterine growth retardation, prematurity, patent ductus arteriosus and foetal death have also been reported but it is not clear whether they are related to the ACE inhibition or the underlying maternal disease.

It is not known whether exposure limited to the first trimester can adversely affect foetal outcome. Women who become pregnant while receiving an ACE inhibitor should be informed of the potential hazard to the foetus.

**Use during lactation**

ACE inhibitors may be excreted in breast milk and their effect on the nursing infant has not been determined. It is recommended that lactating mothers should not breast feed while taking ACE inhibitors.

### 4.7 Effects on ability to drive and use machines

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.
4.8 Adverse reactions

The following adverse reactions have been observed associated with ACE inhibitors therapy

**Cardiovascular system**  Severe hypotension has occurred after initiation or increase of therapy. This occurs especially in certain risk groups (see Warnings and precautions for use). Symptoms like dizziness, feeling of weakness, impaired vision, rarely with disturbance of consciousness (syncope) can occur.

Individual cases of tachycardia, palpitations, arrhythmias, angina pectoris, myocardial infarction, transient ischaemic attacks and cerebral haemorrhage have been reported for ACE inhibitors in association with hypotension.

**Renal system**  Renal insufficiency may occur or be intensified. Acute renal failure has been reported (see Warnings and precautions for use)

**Respiratory system**  ACE inhibitors have been documented to induce cough in a substantial number of patients. Rarely dyspnoea, sinusitis, rhinitis, glossitis, bronchitis and bronchospasm have been reported. In individual cases angioneurotic oedema involving the upper airways has caused fatal airway obstruction.

**Gastro-intestinal tract**  Occasionally nausea, abdominal pain, indigestion, vomiting, diarrhoea, constipation and dry mouth can occur.

Individual cases of cholestatic icterus, hepatitis, pancreatitis and ileus have been described in relation to therapy with ACE inhibitors.

**Skin, vessels**  Occasionally allergic and hypersensitivity reactions can occur like rash, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermic necrolysis, psoriasis like efflorescences, alopecia. This can be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA-titres. ACE inhibitors have been associated with the onset of angioneurotic oedema in a small subset of patients involving the face and oropharyngeal tissues.

**Nervous system**  Occasionally headaches, dizziness, weariness, rarely depressions, sleep disorders, paraesthesias, impotence, disorders of balance, confusion, tinnitus, blurred vision and taste disturbances.

**Product/Laboratory parameters**  Increases in blood urea and plasma creatinine, reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension.

Decreases in haemoglobin, haematocrit, platelets and white cell count, and in individual cases agranulocytosis or pancytopenia, as well as elevation of liver enzymes and serum bilirubin have been reported in a few patients. In patients with a congenital deficiency concerning G-6-PDH individual cases of haemolytic anaemia have been reported.

4.9 Symptoms and treatment of overdosage

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

After ingestion of an overdose, the patients should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake and hasten elimination should be applied if ingestion is recent.
hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The beneficial effects of ACE inhibitors in hypertension and in heart failure appear to result primarily from the suppression of the plasma renin-angiotensin aldosterone system. Renin is an endogenous enzyme synthesised by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin I a relatively inactive decapetide. Angiotensin I is then converted by angiotensin converting enzyme, a peptidyldepeptidase, to angiotensin II. Angiotensin II is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to reduced aldosterone secretion. Although the latter decrease is small, small increases in serum potassium concentrations may occur, along with sodium and fluid loss. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity.

Another function of the converting enzyme is to degrade the potent vasoconstrictory kinin peptide bradykinin to inactive metabolites. Therefore inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin -system which contributes to peripheral vasodilation by activating the prostaglandin system. It is possible that this mechanism is involved in the hypotensive effect of ACE inhibitors and is responsible for certain adverse reactions.

In patients with hypertension administration of ACE inhibitors results in a reduction of supine and standing blood pressure to about the same extent with no compensatory increase of the heart rate. Peripheral arterial resistance is reduced with either no change or an increase in cardiac output.

There is an increase in renal blood flow and glomerular filtration rate is usually unchanged. Achievement of optimal blood pressure reduction may require several weeks of therapy in some patients. The antihypertensive effects are maintained during long term therapy. Abrupt withdrawal of therapy has not been associated with a rapid increase in blood pressure.

ACE inhibitors are effective even in patients with low-renin hypertension. Although antihypertensive effects have been found in the races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to ACE inhibitor monotherapy than non-black patients. This difference disappears when a diuretic is added. The haemodynamic effects of ACE therapy in patients with heart failure result from both arteriolar and venodilatation. Systemic vascular resistance is decreased and venous capacity increased. Thus, pre- and after- load are reduced. Consequences are a decrease in left ventricular filling pressure/capillary wedge pressure and an increase in cardiac output; heart rate remains unchanged or may even decrease. Clinically, signs and symptoms of the heart failure will improve and exercise capacity increase. These effects are maintained during long-term treatment.
5.2 Pharmacokinetic properties

ACE inhibitors can be differentiated into two classes; ACE inhibitors not requiring metabolic activation to be effective and ACE inhibitors requiring conversion to their pharmacologically active form, a process accomplished in the liver (prodrugs).

The most relevant pharmacokinetic properties with regard to absorption, distribution, metabolism and elimination should be mentioned. If the ACE-inhibitor is a prodrug which is hydrolysed in the body to one or more active metabolites should be discussed. Affinity to the circulating ACE and dissociation half life should be indicated.

Special attention should be paid to changes of pharmacokinetic parameters in patients with renal and hepatic insufficiency, the elderly and if appropriate, patients with heart failure. The influence of food on bioavailability should be discussed.