Acuitel®

(quinapril hydrochloride)

1. NAME OF THE MEDICINAL PRODUCTS

Acuitel® 5 mg
Acuitel® 10 mg
Acuitel® 20mg
Active ingredient: quinapril hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Acuitel 5 mg
One film-coated tablet contains
5.416 mg quinapril hydrochloride (corresponds to 5 mg quinapril)
Acuitel 10 mg
One film-coated tablet contains
10.832 mg quinapril hydrochloride (corresponds to 10 mg quinapril)
Acuitel 20 mg
One film-coated tablet contains
21.664 mg quinapril hydrochloride (corresponds to 20 mg quinapril)
For other ingredients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- essential hypertension
- heart failure - add-on to diuretics, and especially in serious heart failure also to digitalis

4.2 Posology and method of administration

Dosage
Note
At the start of therapy with Acuitel, there may be excessive decrease in blood pressure especially in patients with salt and/or fluid deficiency (such as vomiting, diarrhea, diuretic therapy), cardiac insufficiency, acute myocardial infarction, unstable angina pectoris or serious hypertension.
If possible, salt and/or fluid deficiency should be corrected prior to starting Acuitel therapy, diuretic therapy should be reduced or withdrawn if appropriate. In these patients, therapy should be started with the lowest single dose of 2.5 mg quinapril in the morning and blood pressure carefully monitored.
After administration of the first dose, and also when the dose of quinapril and/or loop diuretics is increased, these patients must be medically monitored for at least 6 hours in order to avoid uncontrolled hypotensive reaction.
Adjustment of Acuitel therapy must be made in hospital for patients with malignant hypertension or serious heart failure.
In other cases, the following dosing guidelines apply unless otherwise prescribed:
Essential hypertension.
Usually the initial dose is 10 mg quinapril/day. If this dose does not result in normalization of blood pressure, the dose may be increased to 20 mg/day. The daily dose may be taken all at once or divided into two single doses (in the morning and evening). A dose increase should not be made for a period of 3 weeks. The maintenance dose is usually 10 mg/day, the maximum dose 2x20 mg/day.
Heart failure.
Acuitel may be administered as add-on medication to existing therapy with diuretics and digitalis. The initial dose is 2.5 mg quinapril in the morning and evening. A dose increase should only be made stepwise depending on the patient's individual response to therapy. The maintenance dose is usually 10-20 mg quinapril/day, the maximum dose should not exceed 2x20 mg quinapril/day.
Dosing in moderately impaired renal function (creatinine clearance 30-60 ml/min) and patients older than 65 years of age.
The initial dose is 5 mg quinapril, the maintenance dose usually 5-10 mg quinapril/day.
The maximum dose should not exceed 20 mg quinapril/day.
Dosing in severely impaired renal function (creatinine clearance 10-30 ml/min)
The initial dose is 2.5 mg quinapril (corresponding to 1/2 film-coated tablet Acuitel 5), the maintenance dose is usually also 2.5 mg quinapril/day (corresponding to 1/2 film-coated tablet Acuitel 5). The maximum dose is 5 mg quinapril/daily (corresponding to 1 film-coated Acuitel 5 tablet). The interval between two doses should be at least 24 hours due to the prolonged half-life.
Acuitel is available as scored film-coated tablet to facilitate individual dosing.
Mode and duration of administration
Acuitel may be taken independent of mealtimes, the daily dose may be taken all at once or divided into two single doses.
The physician must determine the duration of administration.

4.3 Contraindications

Acuitel must not be used in:
- hypersensitivity to the medicinally active ingredient or any of the excipients
- known history of angioneurotic edema or other angioedemas (for example resulting from previous ACE-inhibitor therapy)
- stenosis of the renal arteries (both sides, or one-sided in single kidney)
- status following kidney transplantation
- hemodynamically relevant aortic or mitral valve stenosis or hypertrophic cardiomyopathy
- primary hyperaldosteronism
- pregnancy
- lactation (cf. chapter 4.6)

During Acuitel therapy, dialysis or hemofiltration may not be made with polyacrylnitril-methallylsulfonate high-flux membranes (such as AN 69), since there is danger of hypersensitivity reactions (anaphylactoid reactions) up to life-threatening shock during dialysis treatment or hemofiltration.
If emergency dialysis or hemofiltration is necessary, a switch must first be made to another drug against hypertension or heart failure, which may not be an ACE inhibitor, or a different dialysis membrane must be used (see Warnings).
Life-threatening hypersensitivity reactions may occur during LDL (low-density lipoprotein) apheresis (in serious hypercholesterolemia) with dextransulfate if an ACE inhibitor is administered.
Sometimes life-threatening hypersensitivity reactions (such as decrease in blood pressure, shortness of breath, vomiting, allergic skin reactions) may occur during treatment to reduce or eliminate the allergic reaction readiness (desensitization therapy) to insect toxins (such as bee or wasp stings) in concurrent administration of an ACE inhibitor.
If LDL apheresis or desensitization therapy to insect toxins is necessary, the preparation should be replaced by another drug against hypertension or heart failure.

4.4 Special warnings and special precautions for use

Warning
Do not use Acuitel together with polyacrylnitril-methallylsulfonate high-flux membranes (such as AN 69), during LDL apheresis with dextransulfate or during desensitization therapy to insect toxins (cf. Contraindications).
Patients with the rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Acuitel.
Special precautions
Since therapy experience in the following is inadequate, Acuitel must not be used in:
- very serious impairments of renal function (creatinine clearance less than 10 ml/min)
- dialysis patients
- primary liver disease or liver failure
- children.

Acuitel may be used only after very critical benefit-risk assessment under regular controls of representative clinical and laboratory-chemical parameters in:
- serious kidney function impairment (creatinine clearance between 10-30 ml/min)
- clinically relevant proteinuria (more than 1 g/day)
- clinically relevant electrolyte imbalances
- presence of impaired immunoreaction or collagen disease (such as Lupus erythematodes, sclerodermia)
- concurrent systemic therapy with drugs which suppress defense mechanisms (such as corticoids, cytostatics, antimetabolites), allopurinol, procainamide or lithium.

Note: (see dosage)
Renal function must be examined prior to administering Acuitel.
Especially at the start of therapy, Acuitel should only be used under intensive monitoring of blood pressure and/or representative laboratory parameters in:
- patients with salt and/or fluid deficiency
- patients with limited kidney function
- patients with serious hypertension
- patients older than 65 years of age
- patients with serious heart failure (cardiogenic shock)

Cough
During the administration of ACE inhibitors, including quinapril, cough has been reported, which is typically unproductive and consistent and spontaneously regresses upon discontinuation of therapy. Accordingly, cough induced by ACE inhibitors should be considered in the differential diagnosis of cough.
Angioedema
Head and neck angioedema:
Angioedema has been reported in patients treated with ACE inhibitors, with a frequency of 0.1% for quinapril. If laryngeal stridor or angioedema of the face, tongue, or glottis occur, treatment with quinapril should be discontinued immediately. The patient should be treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment. Antihistamines may be useful in relieving symptoms. Angioedema associated with laryngeal involvement may be fatal. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate emergency therapy, including, but not limited to subcutaneous adrenalin (epinephrine) solution 1:1000 (0.3 to 0.5 mL), should be promptly administered.
Intestinal angioedema:
Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting). In some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery. Symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions have been observed between Acuitel or other ACE inhibitors in concurrent administration with:
- table salt: reduction of the hypotensive effect of Acuitel.
- antihypertensives: potentiation of the hypotensive effect of Acuitel, especially with diuretics
- analgesics, antiphlogistics (such as acetylsalicylic acid, indomethacine): possible reduction of the hypotensive effect of Acuitel
- potassium, potassium-sparing diuretics (such as spironolactone, amiloride, triamterene): greater increase in serum potassium concentration
- lithium: elevation of the serum lithium concentration (regular controls!), thus potentiation of the cardio- and neurotoxic effect of lithium
- alcohol: increased alcohol effect
- allopurinol, cytostatics, immunosuppressives, systemic corticoids, procainamide: decrease in leukocyte count in the blood (leukopenia)
- narcotics, anesthetics: potentiated decrease in blood pressure (inform the anesthetist of Acuitel therapy)
- oral antidiabetics (such as sulfonylurea/biguanide), insulin: potentiation of the hypotensive effect by Acuitel.
- neuroleptics, imipramine: potentiation of the hypotensive effect of Acuitel tetracyclines and other active substances reacting with magnesium: reduced absorption.

4.6 Pregnancy and lactation

Experience with humans is inadequate with respect to the safety of use during pregnancy. Cases of a fetal syndrome have been described in recent years for ACE inhibitors, characterized by serious hypoplasia of the skull bones, retarded intrauterine growth, oligohydramnia and neonatal anuria, and which may lead to the death of the neonate. The hypotensive effect on the fetus during the second and third trimester of pregnancy is considered to be the cause. If a switch is made to other antihypertensive medications in the first trimester of pregnancy, no such effects are to be expected.
Prior to the use of an ACE inhibitor like Acuitel, pregnancy must be ruled out in women of child-bearing potential. During Acuitel treatment, these women must use suitable contraceptive measures. If, however, pregnancy is determined during Acuitel treatment, a switch must be made under medical supervision to another possible therapy with less risk for the child, since the child may suffer damage if Acuitel is taken, especially during the final 6 months of pregnancy.
If a nursing mother requires treatment, the infant must be weaned, since ACE inhibitors, including quinapril, pass into breast milk to a limited extent (cf. Contraindications!).

4.7 Effects on ability to drive and use machines

Treatment of hypertension with this drug requires regular medical control. Due to the different individual reactions, the ability to operate a motor vehicle or machinery may be impaired. This applies especially at the start of treatment, if the preparation is changed, and in conjunction with alcohol.

4.8 Undesirable effects

The following adverse events have been observed during therapy with Acuitel or other ACE inhibitors:
The mentioned frequencies comply with the following incidences:
very common (> 10%), common (1-10 %), uncommon (0.1-1 %), rare (0.01-0.1 %), and very rare (< 0.01 % including individual cases).
General disorders
Common: chest pain
Uncommon: anaphylactoid reactions, photosensitivity
Cardiovascular disorders
Common: Especially at the start of Acuitel therapy and in patients with salt and/or fluid deficiency (for example due to vomiting, diarrhea, prior diuretic therapy), heart failure or serious hypertension, but also if the dose of Acuitel and/or diuretics is increased, there may be excessive decrease in blood pressure (hypotension, orthostasis) with symptoms like dizziness, feeling of weakness, blurred vision, rarely accompanied by loss of consciousness (syncope).
Rare: angina pectoris, palpitations, tachycardia, vasodilation, edema
Very rare: cardiac arrhythmias, myocardial infarction, TIA, cerebral insult
Gastrointestinal disorders
Common: nausea, vomiting, diarrhea, (upper) abdominal pain, dyspepsia, pharyngitis, impaired digestion
Rare: dry mouth, dry throat, flatulence, pancreatitis, constipation, anorexia
Very rare: ileus.
Blood and lymphatic system disorders
Uncommon: thrombocytopenia
Psychiatric disorders / nervous system disorders
Common: headache, giddiness, exhaustion, insomnia, paresthesias, tiredness
Uncommon: depression, nervousness, somnolence, vertigo, sleeping disorders, tingling, impaired equilibrium, confusion, tinnitus, blurred vision, changes in taste or transient loss of taste
Skin and subcutaneous tissue disorders
Common: allergic skin reactions such as exanthema
Uncommon: alopecia, excessive sweating, pemphigus, pruritus, angioneurotic edema involving the lips, face and/or extremities (very rarely with involvement of larynx, throat and/or tongue (see emergency measures)), uritcaria, exfoliative dermatitis
Very rare: serious skin reactions like erythema multiforme, psoriasiform skin changes, flush, diaphoresis, onycholysis, potentiation of Raynaud symptoms.
If a serious skin reaction is suspected, the physician must be consulted at once and therapy with Acuitel withdrawn if appropriate.
Note: There is an elevated risk of angioneurotic edema in black patients.
Skin changes may be associated with fever, muscle and joint pain (myalgias, arthralgias, arthritis), vascular inflammation (vasculitis), inflammations of serous tissues and certain changes in laboratory values (eosinophilia, leukocytosis and/or elevated ANA titer, elevated ESR).
Renal and urinary disorders
Common: impairment of kidney function
Uncommon: urinary tract infections, impotence, proteinuria (sometimes with concurrent deterioration of kidney function)
Very rare: acute kidney failure
Eye disorders
Uncommon: amblyopia
Musculoskeletal disorders
Common: back pain
Respiratory disorders
Common: irritative cough, dyspnea
Uncommon: eosinophilic pneumonia
Rare: glossitis, thirst
Very rare: bronchospasm
Hepato-biliary disorders
Uncommon: hepatitis
Very rare: cholestatic icterus or impaired liver function (therapy with the ACE inhibitor is to be withdrawn if icterus occurs or there is a marked increase in hepatic enzymes).
Laboratory values
Common: decrease in hemoglobin concentration, hematocrit, leukocyte or thrombocyte count as well as, especially in patients with impaired renal function, increase in serum concentrations of urea, creatinine and potassium, decrease in serum concentrations of sodium
Uncommon: especially in patients with limited renal function, collagen diseases or concurrent therapy with allopurinol, procainamide or certain drugs which suppress the defense reactions, hyperkalemia, anemia, thrombocytopenia, hemolytic anemia, neutropenia, eosinophilia. Rarely, even agranulocytosis or pancytopenia may occur.
Very rare: hemolysis, increase in bilirubin and hepatic enzyme concentrations.
Hemolysis/hemolytic anemia, also in conjunction with G-6-PDH deficiency has been reported in isolated cases, whereby a causal relationship to the ACE inhibitor could not be established.
An increase in serum potassium has been observed in patients with diabetes mellitus. The excretion

of protein in urine may occur.
Notes
The above laboratory values should be monitored prior to and at regular intervals during Acuitel therapy. Especially at the start of therapy and in risk patients (patients with kidney insufficiency, collagen diseases, under treatment with immunosuppresives, cytostatics, allopurinol, procainamide, digitalis glycosides, glucocorticoids, laxatives, or elderly patients), controls of serum electrolytes and serum creatinine concentrations and blood counts should be performed at short intervals.
If symptoms like fever, lymph node swelling and/or inflammation of the throat should occur during Acuitel therapy, the white blood count should be checked at once.
4.9 Overdose
a) Symptoms of intoxication
The following symptoms are possible, depending on the extent of overdosing: serious hypotension, bradycardia, cardiovascular shock, electrolyte imbalance, kidney failure.
b) Therapy of intoxication
a) The following emergency measures are recommended in the event of life-threatening angioneurotic edema involving the tongue, glottis and/or larynx :
Immediate subcutaneous administration of 0.3-0.5 mg epinephrine or slow intravenous administration of 0.1 mg epinephrine (follow the dilution instructions!), under control of ECG and blood pressure; subsequent systemic administration of glucocorticoids.
Intravenous administration of antihistamines and H2 receptor antagonists is also recommended.
In addition to the use of epinephrine, administration of C1 inactivators may be considered in the case of known C1 inactivator deficiency.
b) Therapeutic measures in overdosing or intoxication depend on the route and time of administration as well as the nature and severity of the symptoms.
In addition to general measures to eliminate quinapril (such as gastric lavage, administration of absorbents and sodium sulfate within 30 minutes after quinapril was taken), the vital parameters must be monitored or corrected under intensive-medical conditions. Quinapril is hardly dialysable.
In hypotension, saline and volume substitution should first be made, if there is no response, catecholamines should in addition be administered intravenously. Therapy with angiotensin II may be considered.
Pace-maker therapy should be performed in case of therapy-refractive bradycardia.
Electrolyte and creatinine concentrations in serum should be continuously monitored.
5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
angiotensin converting enzyme inhibitor
ATC code
C09AA06
Quinapril is hydrolyzed in the liver to quinaprilat, which is an inhibitor of the angiotensin converting enzyme (ACE). The angiotensin converting enzyme (ACE) is a peptidyldipeptidase, which converts angiotensin I to the vasoconstricting substance angiotensin II.
Inhibition of ACE leads to reduced formation of the vasoconstricting angiotensin II in tissue and plasma, whereby aldosterone secretion is reduced, thus permitting an increase in serum potassium concentration. Elevated plasma renin activity results from the elimination of the negative back-coupling of angiotensin II to renin secretion.
Since ACE also metabolizes bradykinine, a vasodepressive peptide, increased activity of circulating and local callikrein-kinine systems (and thus activation of the prostaglandin system) result from inhibition of ACE. It is possible that this mechanism is involved in the antihypertensive effect of ACE inhibitors and is partially responsible for certain adverse effects.
Moreover, it has been clinically demonstrated that quinapril reduces acetylcholine-induced vasoconstriction, an indication of improvement in endothelial dysfunction.
A further effect, of which the mechanism has not yet been elucidated, is the elevation of insulin sensitivity.
Pharmacodynamics
In hypertensive patients, quinapril produces reduction of blood pressure supine and standing, without a compensating increase in heart rate.
In hemodynamic studies, quinapril produces a marked reduction in peripheral arterial resistance. Usually, there was no clinically relevant changes in renal plasma flow and glomerular filtration rate.
In most patients, the onset of antihypertensive effect was observed about 1 hour after oral administration, the maximum effect is usually attained after 2-4 hours.
The maximum hypotensive effect of a defined quinapril dose was usually apparent after 3-4 weeks. The antihypertensive effect is maintained by the recommended daily dose even during long-term therapy.
Brief withdrawal of quinapril dose not result in rapid, excessive increase in blood pressure (rebound effect).
Hemodynamic studies on patients with heart failure showed that quinapril produces a decrease in peripheral systemic resistance and elevation of venous capacity. This results in reduction of the pre- and afterload of the heart (decrease in ventricular filling pressures). Moreover, an increase in cardiac output, stroke index and exercise capacity has been observed under treatment with quinapril.
5.2 Pharmacokinetic properties
Pharmacokinetics
Following oral administration of quinapril, maximum quinapril concentrations are observed within 1 hour. Food consumption has no effect on quinapril absorption. After absorption, quinapril is rapidly and almost completely metabolized to the actually active main metabolite quinaprilat. In addition, some other quantitatively unimportant and pharmacologically inactive metabolites are formed. Maximum plasma levels of quinaprilat, the active metabolite, are observed about 2-3 hours after oral administration of quinapril. Protein binding of quinapril and quinaprilat is about 97 %. About 60 % of a quinapril dose are eliminated via the kidneys, 40 % with feces. Quinaprilat is eliminated primarily via the kidneys; the plasma half-life is about 3 hours, the dissociation half-life from ACE about 26 hours. In patients with renal insufficiency, normal quinapril and quinaprilat plasma curves are measured up to creatinine clearance of 60 ml/min. If creatinine clearance is less than 60 ml/min, the quinaprilat levels increase, the time to occurrence of plasma level maximum is prolonged, the elimination half-life is also prolonged.
Pharmacokinetic studies on patients with terminal kidney disease, undergoing chronic hemodialysis or treated with outpatient peritoneal dialysis, showed that dialysis has only a slight influence on the elimination of quinapril and quinaprilat. The elimination of quinaprilat is also slower in elderly patients (older than 65 years of age) and in patients with serious heart failure. The slowing correlates with limitation of the renal function, which is often present in elderly patients. Patients with moderately limited renal function (creatinine clearance 30-60 ml/min) or severely limited renal function (10-30 ml/min), and in elderly patients, it may therefore be necessary to reduce the quinapril dose.
Bioavailability
Based on recovery studies in urine, quinapril absorption following oral administration is about 60 %.
5.3 Preclinical safety data
Acute toxicity
The LD50 values following oral administration of quinapril were 1440-2150 mg/kg in mice and 3541-4280 mg/kg in rats. The values following intravenous administration were 504-523 mg/kg (mice) and 107-300 mg/kg (rats).
Chronic toxicity
Chronic toxicity was examined in rats and dogs using doses up to 100 mg/kg for 1 year. Weight loss, elevated serum BUN, renin and a decrease in glucose values were found. The heart weights were reduced, the kidneys showed degenerative changes and juxtaglomerular hypertrophy or hyperplasia.
The dog studies showed similar results. Here, too, an increase in plasma renin values and juxtaglomerular hypertrophy was observed. Under the highest doses, the serum BUN values and the hepatic enzyme values were elevated in some animals.
Some animals had gastric erosions, in the highest dose group, focal inflammations were observed in the liver. The changes in kidneys observed in rats and dogs given very high doses are typical for ACE inhibitors and do not appear to be the result of a direct toxic effect, but an excess pharmacological effect (conspicuous prolonged hypotension, stimulation of cells containing renin).
Tumorigenic and mutagenic potential
No tumorigenic effects were observed in studies on rats and mice with daily doses of 75 or 100 mg/kg. Quinapril has been sufficiently examined for mutagenic potential. There was no relevant evidence of mutagenic potential. Quinapril also showed no mutagenic properties in the Ames test with and without metabolic activation. Quinapril had no mutagenic effect in vitro or in vivo in extensive testing in gene and chromosome mutation tests.
Reproduction toxicity
Studies on rats with doses up to 300 mg/kg/day and rabbits up to 1.5 mg/kg/day brought no evidence of a teratogenic potential. While no embryotoxic effects were observed in rats, dam-toxic and embryotoxic effects were observed in rabbits starting at a dose of 1 mg/kg/day. In administration during fetal development and lactation, the growth of the rat offspring was retarded starting at doses of 25 mg/kg/day.
No detriment to fertility was observed in parent animals or offspring.
No experience has been gained in the administration to pregnant women. Retarded growth in utero, premature birth and persistent Ductus arteriosus have been observed in connection with the use of other inhibitors of the converting enzyme. It has not been clarified whether and to what extent the drug may be responsible for these pathological changes. In rare case, irreversible anuria has been observed in the neonate when the mothers were treated with a combination of ACE-inhibitor and diuretic.
No studies have been made of placental permeability.
6. PHARMACEUTICAL PARTICULARS
6.1 Other ingredients
Candililla wax, crospovidone, gelatin, hyprolose, lactose monohydrate, macrogol 400, magnesium carbonate, magnesium stearate (Ph. Eur.), hypromellose, titanium dioxide (E 171).
6.2 Incompatibilities
No incompatibilities are known so far.
6.3 Shelf life
The product should be used before the expiry date written on the outer carton.
6.4 Special precautions for storage
Do not store above 25°C.
6.5 Nature and contents of container
Acuitel 5
30 film-coated tablets
Acuitel 10
30 film-coated tablets
Acuitel 20
30 film-coated tablets
6.6 Instructions for use and handling
No special instructions.
7. MANUFACTURED BY
Pfizer Manufacturing Deutschland GmbH - Betriebsstätte Freiburg
Mooswaldallee 1 79090 Freiburg / Germany
Under license of Parke-Davis
8. DATE OF REVISION OF THE TEXT
April 2005

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctorís prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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