Acuitel®

Quinapril Hydrochloride

Tablets

Germany

AfME Markets using same as LPD:

Bahrain, Jordan, Kuwait, Lebanon, Oman, UAE

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT(S)

Acuitel® 5
5 mg film-coated tablets

Acuitel® 10
10 mg film-coated tablets

Acuitel® 20
20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Quinapril hydrochloride

Acuitel® 5:
Each film-coated tablet contains
5.416 mg quinapril hydrochloride (corresponds to 5 mg quinapril)

Acuitel® 10:
Each film-coated tablet contains
10.832 mg quinapril hydrochloride (corresponds to 10 mg quinapril)

Acuitel® 20:
Each film-coated tablet contains
21.664 mg quinapril hydrochloride (corresponds to 20 mg quinapril)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Cardiac failure - as adjunctive medication to diuretics, and especially in case of serious cardiac failure also to digitalis

4.2 Posology and method of administration

Posology

Note
At the start of therapy with Acuitel, there may be an excessive decrease in blood pressure especially in patients with salt and/or fluid deficiency (such as vomiting, diarrhoea, diuretic therapy), cardiac failure, acute myocardial infarction, unstable angina pectoris or serious hypertension.

If possible, salt and/or fluid deficiency should be corrected prior to starting Acuitel therapy, or current diuretic therapy should be reduced or withdrawn if appropriate.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 cardiac 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 normalisation of blood pressure, the dose may be increased to 20 mg/day. The daily dose may be taken as a single dose or may be divided into two 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 is 20 mg twice daily.

Cardiac failure
Acuitel may be administered as adjunctive medication to existing therapy with diuretics and digitalis. The initial dose is 2.5 mg quinapril in the morning and evening. The dose should only be increased gradually depending on the patient's individual response to therapy. The maintenance dose is usually 10 to 20 mg quinapril/day, the maximum dose should not exceed 20 mg quinapril twice daily.

Dosing in case of moderately impaired renal function (creatinine clearance 30 to 60 ml/min) and patients older than 65 years of age
The initial dose is 5 mg quinapril, the maintenance dose is usually 5 to 10 mg quinapril/day.
The maximum dose should not exceed 20 mg quinapril/day.

Dosing in case of severely impaired renal function (creatinine clearance 10 to 30 ml/min)
The initial dose is 2.5 mg quinapril (corresponding to ½ film-coated tablet Acuitel 5), the maintenance dose is usually also 2.5 mg quinapril/day (corresponding to ½ film-coated tablet Acuitel 5). The maximum dose is 5 mg quinapril/day (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.

Children and adolescents
Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration
Acuitel can be taken independently of meals, the daily dose may be taken as a single dose or may be divided into two doses.

The treating physician must determine the duration of administration.

4.3 Contraindications

Acuitel must not be used in:
- patients with hypersensitivity to the medicinally active substance or any of the excipients listed in section 6.1.
- patients with known history of angioneurotic oedema or other angioedema (e.g. as a result of previous ACE-inhibitor therapy)
- combination with sacubitril/valsartan due to the increased risk of angioedema

- patients with stenosis of the renal arteries (bilateral, or unilateral in the case of a solitary kidney)
- patients with status after kidney transplantation
- patients with haemodynamically relevant aortic or mitral valve stenosis or hypertrophic cardiomyopathy
- patients with primary hyperaldosteronism
- women who are pregnant (see section 4.6)
- women who are breast-feeding (see section 4.6)

The concomitant use of Acuitel and aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or impaired renal function (glomerular filtration rate [GFR] < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

During Acuitel therapy, dialysis or haemofiltration may not be performed with poly(acrylonitrile, sodium-2-methylallylsulphonate)-high-flux membranes (e.g. "AN 69"), since there is a risk for hypersensitivity reactions (anaphylactoid reactions) including life-threatening shock during dialysis treatment or haemofiltration.

If emergency dialysis or haemofiltration is necessary, a switch must therefore first be made to another medicinal product for hypertension or cardiac failure which may not be an ACE inhibitor, or an alternative dialysis membrane must be used (see section 4.4).

Life-threatening hypersensitivity reactions may occur during LDL(low-density lipoprotein) apheresis (in serious hypercholesterolaemia) 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 (desensitisation therapy) to insect toxins (such as bee or wasp stings) and concomitant administration of an ACE inhibitor.

If LDL apheresis or desensitisation therapy to insect toxins is required, the preparation should be temporarily replaced by other medicinal products for hypertension or cardiac failure.

4.4 Special warnings and precautions for use

Warnings
Acuitel should not be used together with poly(acrylonitrile, sodium-2-methylallylsulphonate)-high-flux membranes (e.g. "AN 69") during LDL apheresis with dextran sulfate or during desensitisation therapy to insect toxins (see section 4.3).

Precautions for use
Since therapy experience in the following is inadequate, Acuitel must not be used in case of:
- very serious impairment of renal function (creatinine clearance < 10 ml/min)
- dialysis patients
- primary liver disease or hepatic insufficiency

Acuitel may only be used after very critical evaluation of the benefit-risk ratio and under regular monitoring of representative clinical and laboratory-chemical parameters in case of:
- serious renal function impairment (creatinine clearance between 10 to 30 ml/min)
- clinically relevant proteinuria (> 1 g/day)
- clinically relevant electrolyte imbalances
- presence of impaired immunoreaction or collagen disorder (such as Lupus erythematodes, sclerodermia)
- concurrent systemic therapy with medicinal products that suppress defence mechanisms (such as corticoids, cytostatics, antimetabolites), allopurinol, procainamide or lithium.

Notes (see section 4.2)
Renal function must be examined prior to administering Acuitel.

Especially at the start of therapy, Acuitel should be used only 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 hypertension
- patients over 65 years of age
- patients with cardiac failure (cardiogenic shock)

Dual blockade of the reninangiotensinaldosterone system (RAAS)
There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to close monitoring of renal function, electrolytes and blood pressure.
ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Symptomatic hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving quinapril, hypotension is more likely to occur if the patient has been volume-depleted e.g. due to previous diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see sections 4.5 and 4.8). If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, however, lower doses of Acuitel or any concomitant diuretic therapy should be considered if this event occurs.

Therapy with quinapril under close medical monitoring should be initiated in patients with congestive cardiac failure at risk of excessive decrease in blood pressure. The patients should be closely monitored during the first 2 weeks of therapy and when the dose is increased.

This applies likewise to patients with myocardial ischaemia or cerebrovascular disorders who may experience myocardial infarction or stroke if the blood pressure decreases sharply.

Renal impairment
Changes in renal function can be expected in sensitive patients due to inhibition of the renin angiotensin aldosterone system. In patients with serious cardiac failure whose renal function depends on the activity of the renin angiotension aldosterone system quinalpril therapy may lead to oliguria and/or progressive azotaemia and rarely to acute renal failure and/or death.

In some hypertensive patients or in some patients with cardiac failure without pre-existing kidney disease the BUN and serum creatinine values were increased (> 1.25 times the upper normal limit); the increase was usually slight and transient, especially when quinapril was administered concomitantly with a diuretic. BUN and serum creatinine values were elevated in 2% each of hypertensive patients receiving quinapril monotherapy and in 4% and 3%, respectively, of hypertensive patients under quinapril/HCTZ therapy. This increase occurs more frequently in patients with pre-existing renal failure. It may be necessary to reduce the dose and/or discontinue the diuretic and/or quinapril.

Cough
Cough has been reported with the use of ACE inhibitors including quinapril. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. Accordingly, ACE inhibitor-induced cough should also be considered as part of the differential diagnosis of cough.

Hypersensitivity reactions

Hypersensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma, e.g. purpura, photosensitivity, urticaria, necrotising angiitis, dyspnoea including pneumonitis and pulmonary oedema, anaphylactic reactions.

Angioneurotic oedema

Head and neck angioedema:

Angioneurotic oedema has been reported in patients treated with ACE inhibitors, with a frequency of 0.1% for quinapril. If wheezing or angioneurotic oedema of the face, tongue, or glottis occurs, treatment with quinapril should be discontinued immediately. The patient should be treated appropriately in accordance with accepted medical care, and observed closely 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. Angioneurotic oedema 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 1:1,000 (0.3 to 0.5 ml), should be promptly administered.

The combination of quinapril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3).

Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of quinapril therapy. If treatment with sacubitril/valsartan is stopped, quinapril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE inhibitors may also increase the risk of angioedema (see section 4.5). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on quinapril.

Patients taking concomitant mTOR(mammalian Target of Rapamycin) inhibitor (e.g. temsirolimus) or concomitant DPP-IV(dipeptidyl-peptidase-4) inhibitor (e.g. vildagliptin) therapy may be at increased risk for angioneurotic oedema. Special caution should be used when starting an mTOR inhibitor or a DPP-IV inhibitor in a patient already taking an ACE inhibitor.

Intestinal angioneurotic oedema

Intestinal angioneurotic oedema has been reported in patients treated with ACE inhibitors. These patients complained about abdominal pain (with or without nausea or vomiting). In some cases there was no previous history of facial angioneurotic oedema and C-1 esterase levels were normal. The angioneurotic oedema was diagnosed by procedures including abdominal CT scan, ultrasound, or during surgery. Symptoms resolved after stopping the ACE inhibitor. Intestinal angioneurotic oedema should be included in the differential diagnosis of patients on ACE inhibitors complaining about abdominal pain.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Ethnic differences

Black patients receiving ACE-inhibitor therapy have been reported to have a higher incidence of angioedema compared to non-black patients. Clinical studies have also revealed that the effect on blood pressure is less pronounced in black patients than in non-blacks.

Neutropenia/Agranulocytosis

Treatment with ACE inhibitors has been rarely associated with agranulocytosis and bone marrow depression in patients with hypertension but more frequently in patients with renal impairment, especially if they also have collagenosis.

Agranulocytosis has been rarely reported during treatment with quinapril. Monitoring of white blood cell counts in patients with collagenosis and/or renal disease should therefore be considered.

Hyperkalaemia
Serum potassium levels may be increased in patients receiving quinapril alone. Because of the risk of further potentiating increases in the serum potassium levels it is advised that combination therapy with potassium-sparing diuretics or other medicinal products that may increase the serum potassium level be initiated with caution and the patient's serum potassium levels be closely monitored (see section 4.5). When administered concomitantly quinapril may therefore weaken hypokalaemia caused by thiazide diuretics.

Hyponatraemia and Syndrome of Inappropriate Anti-diuretic Hormone (SIADH)
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with other ACE inhibitors. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

Alteration of hepatic parameters
Rarely, ACE inhibitors have been associated with a syndrome beginning with cholestatic jaundice and progressing to a fulminant hepatic necrosis (in some cases fatal). Patients who during ACE inhibitor therapy experience jaundice or clearly elevated hepatic enzymes, should discontinue quinapril and receive appropriate medical follow-up.

Diabetic patients
In diabetic patients, ACE inhibitors may enhance insulin sensitivity and have been associated with hypoglycaemia in patients treated with oral antidiabetic agents or insulin. Glycaemic levels should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

Surgery/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, quinapril may block angiotensin II formation due to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion (see section 4.5).

Pregnancy
Patients intending to become pregnant should be switched to an alternative antihypertensive treatment which has an established safety profile for the use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and alternative therapy should be started, if needed (see sections 4.3 and 4.6).

Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Acuitel.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions have been observed between Acuitel or other ACE inhibitors during concomitant administration with:
- Table salt: reduction of the hypotensive effect of Acuitel
- Antihypertensives: potentiation of the hypotensive effect of Acuitel, especially with diuretics
- Analgesics. non-steroidal antiphlogistics (NSAIDs including COX[cyclooxygenase]-2 inhibitors): Treatment with NSAIDs (including COX-2 inhibitors) may attenuate the antihypertensive effect of ACE inhibitors. NSAIDs (including COX-2 inhibitors) and ACE inhibitors have additive effects regarding an increase in serum potassium and may result in deterioration of renal function. This is usually reversible. In rare cases, acute renal failure may occur, in particular, in patients with compromised renal function, elderly patients or patients who are volume-depleted (including those on diuretic therapy).
- Diuretics: enhancement of the hypotensive effect of Acuitel (reduction of the initial dose of Acuitel and medical supervision of the patient for up to two hours following the 1st Acuitel dose)
- Lithium: elevation of the serum lithium concentration (regular monitoring!), thus potentiation of the cardio- and neurotoxic effect of lithium
- Alcohol: increased alcohol effect, potentiation of orthostatic hypotension
- Allopurinol, cytostatics, immunosuppressives, systemic corticoids, procainamide: decrease in leukocyte count in the blood (leukopenia)
- Anaesthetics: potentiated decrease in blood pressure (inform the anaesthetist of Acuitel therapy)
- Oral antidiabetics (such as sulfonylurea/biguanide), insulin: potentiation of the blood sugar-reducing effect by Acuitel (regular monitoring!)
- Neuroleptics, imipramine: potentiation of the hypotensive effect of Acuitel
- Tetracyclines and other active substances reacting with magnesium: reduced absorption
- Gold preparations: nitritoid reactions have been reported rarely in patients on therapy with injectable gold and concomitant ACE inhibitor therapy.
- Barbiturates: potentiation of orthostatic hypotension
- Narcotics: potentiated decrease in blood pressure (inform the anaesthetist of Acuitel therapy), potentiation of orthostatic hypotension
- Antacids: may decrease the bioavailability of quinapril.

Medicinal products that increase the serum potassium concentration
Concomitant treatment with potassium-sparing diuretics (e.g. spironolactone, amiloride, triamterene), potassium salts or medicinal products that increase the serum potassium concentration should be done with caution: stronger increase of the serum potassium concentration (regular monitoring!, see section 4.4). In elderly patients or in patients with impaired renal function, the concomitant ingestion of ACE inhibitors with sulfamethoxazole/trimethoprim has been associated with severe hyperkalaemia. It is assumed that this can be attributed to trimethoprim. Products containing quinapril or trimethoprim should therefore be administered with caution concomitantly and the serum potassium concentration should be monitored regularly.

Dual blockade of the renin angiotensin aldosterone system (RAAS)
Clinical trial data has shown that dual blockade of the reninangiotensinaldosteronesystem (RAAS) through the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared with the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1). Blood pressure, kidney function and electrolytes must be closely monitored in patients receiving quinapril and other active substances that affect the renin angiotensin aldosterone system.

Other drugs known to cause angioedema
Patients taking concomitant mTOR inhibitor (e.g. temsirolimus) or concomitant DPP-IV inhibitor (e.g. vildagliptin) therapy may be at increased risk for angioneurotic oedema. Special caution should be used when starting an mTOR inhibitor or a DPP-IV inhibitor in patients already taking an ACE inhibitor.

NEP inhibitors
The concomitant use of quinapril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of quinapril therapy. Quinapril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4). Concomitant use of other NEP inhibitors (e.g. racecadotril) and quinapril may also increase the risk of angioedema (see section 4.4).

Aliskiren
Do not administer aliskiren with quinapril in diabetic patients or patients with renal impairment (creatinine clearance < 60 ml/min/1.73 m^2).

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of ACE inhibitors is contraindicated during pregnancy (see sections 4.3 and 4.4).
When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if required, alternative therapy should be started.
Treatment with ACE inhibitors during the second and third trimesters of pregnancy is known to induce potential foetotoxic effects (reduced renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). In the case of exposure to ACE inhibitors from the second trimester of pregnancy, ultrasound checks of renal function and skull are recommended.
Infants whose mothers have taken ACE inhibitors should be repeatedly and closely monitored for hypotension (see sections 4.3 and 4.4).

Breastfeeding
Very limited pharmacokinetic data indicate that very low concentrations of Acuitel are found in human milk (see section 5.2). Even though these concentrations seem to be clinically irrelevant, Acuitel should not be used during breastfeeding of preterm infants as well as during the first weeks after delivery as a potential risk of cardiovascular and renal effects in the infant cannot be excluded and no adequate clinical experience for use during breastfeeding is available.

4.7 Effects on ability to drive and use machines

Treatment of hypertension with this medicinal product requires regular medical supervision. Due to individually different reactions, the ability to drive a car or operate machines may be impaired, especially at the beginning of therapy or in case of switch-over to another therapy as well as due to interaction with alcohol.

4.8 Undesirable effects

The frequencies of undesirable effects are based on the following categories:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

The following undesirable effects have been observed during therapy with Acuitel or other ACE inhibitors:

General disorders and administration site conditions

Common:	Chest pain, fatigue, asthenia
Uncommon:	Fever, generalised or peripheral oedema

Immune system disorders

Not known:	Anaphylactoid reactions

Cardiac disorders

Uncommon:	Angina pectoris, palpitations, tachycardia, oedema, myocardial infarction
Very rare:	Cardiac arrhythmias, cerebral insult

Vascular disorders

Common:	Especially at the start of Acuitel therapy and in patients with salt and/or fluid deficiency (for example, due to vomiting, diarrhoea, previous diuretic therapy), cardiac failure or serious hypertension, but also if the dose of Acuitel and/or diuretics is increased, there may be an excessive decrease in blood pressure (hypotension, orthostatic hypotension) with symptoms like dizziness, feeling of weakness, impaired vision, rarely accompanied by loss of consciousness (syncope).
Uncommon:	Vasodilation, TIA
Not known:	Orthostatic hypotension

Gastrointestinal disorders

Common:	Nausea, vomiting, diarrhoea, (upper) abdominal pain, dyspepsia, pharyngitis, impaired digestion
Uncommon:	Dry mouth, dry throat, flatulence, pancreatitis (sometimes fatal), constipation, anorexia
Rare:	Altered taste, glossitis
Very rare:	Ileus, intestinal angioedema

Blood and lymphatic system disorders

Uncommon:	Thrombocytopenia
Not known:	Neutropenia, agranulocytosis, haemolytic anaemia

Psychiatric disorders/nervous system disorders

Common:	Headache, drowsiness, exhaustion, insomnia, paraesthesia, tiredness, dizziness
Uncommon:	Depression, nervousness, somnolence, sleep disturbances, tingling, balance disorders, confusion, transient loss of taste
Rare:	Syncope

Skin and subcutaneous tissue disorders

Common:	Allergic skin reactions such as exanthema

Uncommon:	Alopecia, increased perspiration, pemphigus, pruritus, rash, angioneurotic oedema involving the lips, face and/or extremities (very rarely with involvement of larynx, throat and/or tongue [see emergency measures]), urticaria, photosensitivity
Rare:	Erythema multiforme
Very rare:	Serious skin reactions such as psoriasiform skin changes, flush, diaphoresis, onycholysis, potentiation of Raynaud symptoms
Not known:	Stevens-Johnson syndrome, exfoliative dermatitis, epidermal necrolysis

If a serious skin reaction is suspected, the treating physician must be consulted immediately and therapy with Acuitel withdrawn if appropriate.

Note: There is an elevated risk of angioneurotic oedema in black patients.

Skin changes may be associated with fever, muscle and joint pain (myalgia, arthralgia, arthritis), vascular inflammation (vasculitis), inflammation of serous tissues and certain changes in laboratory values (eosinophilia, leukocytosis and/or elevated ANA titre, elevated ESR).

Renal and urinary disorders

Common:	Renal function disorder
Uncommon:	Urinary tract infection, proteinuria (sometimes with concomitant deterioration of renal function)
Very rare:	Acute renal failure

Reproductive system and breast disorders

Uncommon:	Impotence
Rare:	Erectile dysfunction

Eye disorders

Uncommon:	Amblyopia
Very rare:	Blurred vision

Ear and labyrinth disorders

Uncommon:	Tinnitus, vertigo

Musculoskeletal and connective tissue disorders

Common:	Back pain, myalgia

Respiratory, thoracic and mediastinal disorders

Common:	Cough, irritative cough, dyspnoea, rhinitis
Uncommon:	Sinusitis, upper respiratory tract infection, bronchitis, eosinophilic pneumonia
Rare:	Thirst
Not known:	Bronchospasm

In individual cases, angioneurotic oedema involving upper airways has caused fatal airway obstruction.

Hepatobiliary disorders

Uncommon:	Hepatitis
Very rare:	Cholestatic icterus or impaired hepatic function (therapy with the ACE inhibitor is to be withdrawn if jaundice occurs or there is a marked increase in hepatic enzymes).

Congenital, familial and genetic disorders

See sections 4.3 and 4.6

Investigations

Common:	Decrease in haemoglobin concentration, haematocrit, leukocyte or thrombocyte count as well as, especially in patients with impaired renal function, increase in serum concentrations of urea or creatinine (more likely to appear in patients receiving concomitant diuretic therapy than those on monotherapy with quinapril; often reversible under continued therapy), potassium, decrease of sodium concentrations in serum
Uncommon:	Especially in patients with impaired renal function, collagen disorders or concomitant therapy with allopurinol, procainamide or certain medicinal products which suppress the defence reactions, anaemia, eosinophilia and rarely even pancytopenia may occur.
Very rare:	Haemolysis, increase in bilirubin and hepatic enzyme concentrations
Not known:	Haemolytic anaemia in patients with a G-6-PDH deficiency

An increase in serum potassium has been observed in patients with diabetes mellitus. Increased proteinuria may occur.

Metabolism and nutrition disorders

Common:	Hyperkalaemia
Not known:	Hyponatraemia (see section 4.4)

Notes

The above-mentioned laboratory values should be monitored prior to and at regular intervals during treatment with Acuitel. Particularly upon initiation of treatment and in risk patients (patients with renal impairment, collagen disorders, during treatment with immunosuppressives, cytostatics, allopurinol, procainamide, digitalis glycosides, glucocorticoids, laxatives, or elderly patients), close monitoring of serum electrolyte and serum creatinine concentrations and of the blood count is deemed appropriate at short intervals.

Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with other ACE inhibitors (see section 4.4).

Should symptoms such as fever, lymph node swelling and/or inflammation of the throat occur during Acuitel therapy, the white blood count has to be examined immediately.

Vasculitis and gynaecomastia have been reported with other ACE inhibitors and it cannot be excluded that these unwanted effects are group-specific.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing 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 according to their local country requirements.

4.9 Overdose

The oral LD_{50} of quinapril in mice and rats ranges from 1,440 to 4,280 mg/kg.

No specific information is available on the treatment of overdose with quinapril. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which are normally treated by intravenous volume expansion.

Treatment is symptomatic and supportive, consistent with established medical care.

Haemodialysis and peritoneal dialysis have only little effect on the elimination of quinapril and quinaprilat.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin converting enzyme inhibitor
ATC code: C09AA06

Quinapril is hydrolysed in the liver to quinaprilat, which is an inhibitor of the angiotensin converting enzyme (ACE). 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 metabolises bradykinine, a vasodepressive peptide, increased activity of circulating and local kallicrein-kinine systems (and thus activation of the prostaglandin system) results 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 haemodynamic studies, quinapril produces a marked reduction in peripheral arterial resistance. Usually, there were no clinically relevant changes in renal plasma flow and glomerular filtration rate.
In most patients, the onset of antihypertensive effect was observed approximately 1 hour after oral administration, the maximum effect was usually attained after 2 to 4 hours.
The maximum hypotensive effect of a defined quinapril dose was usually apparent after 3 to 4 weeks. The antihypertensive effect is maintained at the recommended daily dose even during long-term therapy.

Brief withdrawal of quinapril does not result in rapid, excessive increase in blood pressure (rebound effect).

Haemodynamic studies on patients with cardiac failure showed that quinapril produces a decrease in peripheral systemic resistance and elevation of venous capacity. This results in reduction of the pre- and after-load 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.

Two large randomised, controlled trials (ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and VA NEPHRON-D [The Veterans Affairs Nephropathy in Diabetes]) have examined the concomitant use of an ACE inhibitor and an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-

D was a study conducted on patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared with monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and angiotensin II receptor blockers.
ACE inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and particular serious adverse events (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population
A randomised clinical trial over 8 weeks (2 weeks double-blind followed by 6 weeks extension) using target doses of 2.5, 5, 10 and 20 mg of quinapril in 112 children and adolescents with hypertension or high normal blood pressure, failed to reach its primary objective (reduction of diastolic blood pressure after 2 weeks). For systolic blood pressure (secondary objective of efficacy) in week 2 only there was a statistically significant linear dose response across treatments with a significant difference between the quinapril 20 mg administered once daily and the placebo treatment groups.

Long-term effects of quinapril on growth, puberty and general development have not been studied.

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 metabolised 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 approximately 2 to 3 hours after oral administration of quinapril. Protein binding of quinapril and quinaprilat is approximately 97%. Approximately 60% of a quinapril dose are eliminated via the kidneys, 40% with faeces. Quinaprilat is eliminated primarily via the kidneys; the plasma half-life is approximately 3 hours, the dissociation half-life from ACE approximately 26 hours. In patients with renal impairment, normal quinapril and quinaprilat plasma curves were 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 haemodialysis 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 cardiac 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 to 60 ml/min) or severely limited renal function (10 to 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 approximately 60%.

Breastfeeding

Following administration of a single oral dose of 20 mg quinapril to 6 breastfeeding women, the milk/plasma (M/P) ratio for quinapril was 0.12. Quinapril was not detected in breast milk after four hours after dose administration. Quinaprilat milk levels were below detection limits (<5 µg/l) at all timepoints. It is estimated that a breastfed infant would take up approximately 1.6% of the quinapril dose given to the mother.

Paediatric population
The pharmacokinetics of quinapril has been studied in a single-dose study (0.2 mg/kg BW) to 24 children aged 2.5 months to 6.8 years and in a multiple-dose study (0.016 to 0.468 mg/kg BW) to 38 children aged 5 to 16 years with an average weight of 66 kg (schoolchildren) or 98 kg (adolescents). As in adults, quinapril was rapidly converted to quinaprilat. Quinaprilat concentrations generally peaked 1 to 2 hours post dose and declined then again with a mean half-life of 2.3 hours. In infants and young children the exposure following a single dose of 0.2 mg/kg BW is comparable to that observed in adults after a single dose of 10 mg. In the multiple-dose study of school-aged children and adolescents, the AUC and C_{max} values of quinaprilat were observed to increase linearly with increasing dose of quinapril (on a mg/kg BW basis).

5.3 Preclinical safety data

Acute toxicity
The LD_{50} values following oral administration of quinapril were 1,440 to 2,150 mg/kg in mice and 3,541 to 4,280 mg/kg in rats. The values following intravenous administration were 504 to 523 mg/kg (mice) and 107 to 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 study showed similar results. Here, too, an increase in plasma renin values and juxtaglomerular hypertrophy were 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 (markedly 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* and *in vivo* in extensive testing in gene and chromosome mutation tests.

Reproductive 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. When administered during foetal development and breastfeeding, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Candililla wax, crospovidone, gelatin, hyprolose, lactose monohydrate, macrogol 400, heavy alkaline magnesium carbonate, magnesium stearate (Ph.Eur.), hypromellose, titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use ACUITEL after the expiry date which is stated on the carton / Blister after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Keep in a dry place. Do not store above 25°C.

6.5 Nature and contents of container

Blister packs made of a polyamide/aluminium/PVC complex and an aluminium foil.

Acuitel 5
30 film-coated tablets (N1)
100 film-coated tablets (N3)

Acuitel 10
30 film-coated tablets (N1)
100 film-coated tablets (N3)

Acuitel 20
30 film-coated tablets (N1)
100 film-coated tablets (N3)

Not all pack sizes maybe marketed.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment**.**

7. MARKETING AUTHORISATION HOLDER

PFIZER PHARMA PFE GmbH
Linkstr. 10
10785 Berlin
Phone: 0800 8535555

Fax: 0800 8545555

MANUFACUTRED BY

Pfizer Manufacturing Deutschland GmbH
Betriebsstatte Freiburg, Mooswaldallee 1
79090 Freiburg
Federal Republic of Germany

8. DATE OF REVISION OF THE TEXT

August 2017

9. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

To report any side effect(s):	
United Arab Emirates (UAE): Pharmacovigilance section P.O.Box: 1853 Tel: 80011111 Email : pv@moh.gov.ae Drug Department Ministry of Health & Prevention Dubai	**Kuwait:** Website: www.moh.gov.kw/kdfc/ P.O. BOX: 22575, SAFAT 13086 KUWAIT
Jordan: Website : www.jfda.jo Tel: 0096265632000 - 0096264602550 Fax:0096265105916 - 0096265105893 E-mail : info@jfda.jo	**Lebanon :** Website :www.moph.gov.lb
Oman: Web site: www.moh.gov.om Tel: 0096824601044 Fax: 0096824602287 E-mail: mohphar@omantel.net.om	

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 doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are 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 and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists