Accuzide® 20

Quinapril and Hydrochlorothiazide 20 mg/12.5 mg

Film-coated tablets

Reference: Germany

AfME Markets using same as LPD:

UAE- Bahrain-Kuwait-Oman- Lebanon- Jordan

SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: FETAL TOXICITY

•When pregnancy is detected, discontinue Accuzide as soon as possible.

•Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

1. NAME OF THE MEDICINAL PRODUCTS

Accuzide® 20 mg/12.5 mg
Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Quinapril hydrochloride and hydrochlorothiazide

Accuzide 20 mg/12.5 mg:
Each film-coated tablet contains 21.664 mg of quinapril hydrochloride (corresponding to 20 mg of quinapril) and 12.50 mg of hydrochlorothiazide. The film-coated tablet is pink, scored, triangular and biconvex.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

The score line for Accuzide 20 mg/12.5 mg only serves to break the film-coated tablets so that they can be swallowed more easily and not to divide them into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension. Accuzide[1] film-coated tablets are indicated in patients whose hypertension could not be lowered adequately with quinapril alone.

4.2 Posology and method of administration

Posology
As a matter of principle, treatment of hypertension should be started with low doses of a single active substance and increased gradually.

Administration of the fixed combination of Accuzide is recommended only after previous individual dose titration with the individual substances (i.e. quinapril and hydrochlorothiazide). If clinically

[1] All data given for Accuzide apply to Accuzide 10 mg/12.5 mg, Accuzide 20 mg/12.5 mg, and Accuzide 20 mg/25 mg diuplus.

appropriate, a direct change from monotherapy to the fixed combination can be considered.

Note
Since an excessive drop in blood pressure may occur when therapy is changed from quinapril monotherapy to the combination Accuzide - especially in patients with salt and/or fluid deficiency (e.g. in case of vomiting/diarrhoea, prior diuretic treatment), severe hypertension - these patients must be monitored for at least 6 hours.

Accuzide 20 mg/12.5 mg:
The usual daily dose for patients for whom a combination therapy is indicated is 1 film-coated tablet Accuzide 20 mg/12.5 mg (corresponding to 20 mg quinapril and 12.5 mg hydrochlorothiazide) in the morning. A dose of 1 film-coated tablet Accuzide 20 mg/12.5 mg per day should not be exceeded.

Dose in case of moderately impaired renal function (creatinine clearance 30-60 mL/min) and elderly patients (older than 65 years)
The dose adjustment must be made with special caution (titration of the individual components).

Therapy of patients with mild renal impairment (creatinine clearance 30-60 mL/min) should be started with 5 mg quinapril as monotherapy. The maintenance dose usually is 5 to 10 mg quinapril per day. The maximum dose of 20 mg quinapril per day should not be exceeded.

Dose titration with hydrochlorothiazide (HCTZ) should be performed for patients who additionally require a diuretic. Control of blood pressure can then be continued with Accuzide.

Patients with severe renal impairment (creatinine clearance less than 30 mL/min) should not be treated with Accuzide.

Method of administration

Accuzide can be taken independently of meals. The indicated daily quantity should be swallowed whole with plenty of fluid in a single dose in the morning.

The treating physician determines the duration of administration.

4.3 Contraindications

Accuzide must not be used in:
- Patients with hypersensitivity to the active substances or any of the excipients listed in section 6.1, thiazides or sulfonamides (note possible cross reactions),
- Patients with hereditary/idiopathic angioedema or a known history of angioedema (e.g. as a result of previous ACE [angiotensin-converting-enzyme]-inhibitor therapy),
- Combination with sacubitril/valsartan due to the increased risk of angioedema
- Patients with severe renal function disorder (serum creatinine more than 1.8 mg/dL or creatinine clearance less than 30 mL/min),
- Patients on dialysis,
- Patients with renal artery stenosis (bilateral or in the case of a solitary kidney),
- Patients with status after kidney transplantation,
- Patients with anuria,
- Patients with haemodynamically relevant aortic or mitral valve stenosis or hypertrophic cardiomyopathy,
- Patients with decompensated cardiac failure,
- Patients with primary hyperaldosteronism,
- Patients with severe hepatic function disorder (precoma/coma hepaticum) or primary liver disease,
- Patients with clinically relevant electrolyte disturbance (hypercalcaemia, hyponatraemia, hypokalaemia),

- Children (due to a lack of adequate therapeutic experience),
- Women who are pregnant (see section 4.6),
- Women who are breast-feeding (see section 4.6; discontinue breast-feeding!).

Life-threatening hypersensitivity reactions may occur during LDL (low-density lipoprotein)-apheresis (in case of severe hypercholesterolaemia) with dextran sulfate and concurrent administration of an ACE inhibitor.

Sometimes life-threatening hypersensitivity reactions (e.g. blood pressure drop, dyspnea, vomiting, allergic skin reactions) may occur during treatment to reduce or eliminate the tendency to allergic reaction (desensitisation therapy) against insect toxins (such as bee or wasp stings) and the concurrent administration of an ACE inhibitor.

If LDL apheresis or desensitisation therapy to insect toxins is necessary, the preparation must be temporarily replaced with other antihypertensive medicines.

During treatment with Accuzide dialysis or haemofiltration with poly (acrylonitrile, sodium-2-methyl allyl sulfonate)-high-flux-membranes (e.g. "AN 69") must not be performed, since there is the risk during dialysis or haemofiltration that hypersensitivity reactions (anaphylactoid reactions) as severe as life-threatening shock may occur. In case of emergency dialysis or haemofiltration, a switch must therefore be made to another antihypertensive drug – not an ACE inhibitor – in advance or a different dialysis membrane must be used.

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

4.4 Special warnings and precautions for use

Accuzide should not be used with polyacrylonitrile-methallyl sulfonate-high-flux membranes (e.g. "AN 69") during LDL-apheresis with dextran sulfate or during desensitisation treatment against insect toxins (see section 4.3).

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

Accuzide may only be used after a very critical benefit-risk evaluation with regular monitoring of representative clinical and laboratory-chemical parameters for:
- Clinically relevant proteinuria (more than 1 g/day),
- impaired immunological reaction or collagen disorder (e.g. lupus erythematosus, scleroderma),
- Concurrent systemic therapy with medicinal products that suppress the defence reactions (e.g. corticoids, cytostatics, antimetabolites), allopurinol, procainamide, lithium, digitalis glycosides, laxatives,
- Gout,
- Hypovolaemia,
- Cerebrosclerosis,
- Coronary sclerosis,
- Manifest or latent diabetes mellitus,
- Impaired hepatic function.

Notes (see section 4.2)
The renal function must be checked prior to administration of Accuzide. Caution must be exercised in case of concomitant medicinal products that may increase the serum potassium level.

Lithium
Normally, lithium should not be used with diuretics. Diuretic substances decrease renal clearance of lithium and carry a high risk of lithium toxicity (see section 4.5).

A salt/fluid deficiency must be balanced prior to the start of therapy.

Especially at the start of therapy, Accuzide should be used only under intensive blood pressure monitoring and/or representative laboratory parameters in:
- Patients with impaired renal function (serum creatinine up to 1.8 mg/dL or creatinine clearance 30 - 60 mL/min),
- Patients with severe hypertension,
- Patients over 65 years of age.

Dual blockade of the renin angiotensin aldosterone 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.

Corresponding to the administration options of the individual substances, Accuzide may be administered in cases of reduced cardiac performance for which the dose level of the individual substances was previously reached that corresponds to the composition of Accuzide.

Hypotension
Quinapril/HCTZ may lead to symptomatic hypotension, normally not more frequently than for individual substances used in monotherapy. Symptomatic hypotension is rarely observed in patients with uncomplicated hypotension. In hypersensitive patients who receive quinapril it is more likely that hypotension will occur if the patient experienced a volume loss, e.g. during diuretic therapy, dietary sodium restriction, dialysis, diarrhoea or vomiting or if the patient suffers from severe renin-dependent hypertension (see section 4.5).

Quinapril/HCTZ should be used with caution in patients who receive a concomitant therapy with other antihypertensive medicines. The thiazide component of quinapril/HCTZ may increase the efficacy of other antihypertensive medicines, especially of ganglionic or peripheral adrenergic blockers. The antihypertensive efficacy of the thiazide component can also be increased for patients with postsympathectomy.

If symptomatic hypotension occurs, the patient should be placed in recumbent position and, if necessary, receive an intravenous saline infusion. A transient hypotensive reaction should not be regarded as a contraindication to further use; however, lower doses of Accuzide should be considered if this event occurs.

For patients with congestive cardiac failure with and without renal impairment an ACE inhibitor therapy to control hypertension may lead to an excessive drop in blood pressure that may result in oliguria, azotaemia and, in rare cases, in acute renal failure and death. A therapy with quinapril/HCTZ should be initiated under close medical monitoring. Patients should be observed closely during the first 2 weeks of treatment and if the dose is increased.

Cardiac failure/cardiac disorder
As a consequence of the inhibition of the renin-angiotensin-aldosterone system changes in the renal function can be expected in susceptible individuals. In patients with severe cardiac failure whose renal

function could depend on the activity of the renin-angiotensin-aldosterone system oliguria and/or progressive azotaemia and rarely acute renal insufficiency and/or death could occur if treated with quinapril.

In a few patients with hypertension or cardiac failure with no apparent pre-existing kidney disease, an increase in the urea-nitrogen in the blood and serum creatinine was observed (1.25-fold of the upper standard level) that normally was insignificant and transient, especially if quinapril was administered concomitantly with a diuretic. An increase of urea-nitrogen in the blood and serum creatinine was observed, in each case, in 2% of the hypertensive patients using quinapril monotherapy and in 4% and 3%, respectively, of hypertensive patients using quinapril/HCTZ. This increase occurs more frequently in patients with pre-existing renal insufficiency. It may be necessary to decrease the dose and/or discontinue the diuretic and/or quinapril.

Changes of liver values
ACE inhibitors are rarely associated with a syndrome that starts as cholestatic jaundice and develops into fulminant hepatic necrosis (in some cases fatal). Patients who contract jaundice or whose hepatic enzymes increase markedly during ACE inhibitor therapy should discontinue the use of quinapril/HCTZ and undergo appropriate medical aftercare.

Among thiazides, the Stevens Johnson syndrome and exacerbations or the activation of a systemic lupus erythematosus have been reported.

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

Angioedema
Head region:
Angioedema has been observed in patients treated with ACE inhibitors, with a frequency of 0.1% for quinapril. If wheezing or angioedema develops in the face, on the tongue, or glottis, treatment with quinapril must be discontinued immediately. The patient should be treated properly and closely monitored until the swelling disappears. If the swelling is confined to the face and lips, it generally subsides on its own without treatment. Antihistamines may be helpful in relieving the symptoms. An angioedema involving the larynx may be fatal. If the involvement of the tongue, glottis, or larynx is likely to cause airway obstruction, appropriate emergency therapy must be promptly applied (see section 4.9).

Patients with a history of angioedemas that are not associated with ACE inhibitor therapy could be at an increased risk for angioedema if ACE inhibitors are administered to them (see section 4.3).

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 simultaneously receiving an mTOR(mammalian Target of Rapamycin) inhibitor (e.g. temsirolimus) or a DPP-4(dipeptidyl-peptidase-4) inhibitor (e.g. vildagliptin) for therapeutic purposes may be at increased risk of angioneurotic oedema. Special care is required if patients already receiving an ACE inhibitor begin a course of treatment with an mTOR inhibitor or a DPP-4 inhibitor**.**

Intestinal angioedema:
Intestinal angioedema has been observed in patients treated with ACE inhibitors. These patients complained of abdominal pain (with or without nausea or vomiting). In a few cases there was no prior history of facial angioedema and the C-1 esterase levels were normal. The angioedema was diagnosed, for example, in an abdominal CT scan, ultrasound, or during surgery. Symptoms reversed themselves after the ACE inhibitor was discontinued. Intestinal angioedema should be included in the differential diagnosis if patients using ACE inhibitors complain of abdominal pain.
The use of Accuzide may yield positive results in doping tests. Using Accuzide as a doping agent may constitute a health hazard.

Ethnic differences
Angioedema occurred more frequently in black-skinned patients with who received ACE inhibitor therapy than in patients with other skin types. It should also be pointed out that in controlled clinical studies the effect of ACE inhibitors on the blood pressure of black-skinned patients was reduced compared to patients with other skin types.

Serum electrolyte disturbances
Patients who are given quinapril/HCTZ should be monitored for clinical signs of thiazide-induced liquid or electrolyte disturbances. The serum electrolytes of these patients should be checked regularly (especially sodium and potassium). Since quinapril reduces the production of aldosterone its combination with hydrochlorothiazide may reduce hypokalaemia induced by diuretics.

In many patients, the opposite effects of quinapril and hydrochlorothiazide on the serum potassium level balance themselves approximately in such a way that there is no apparent net effect on the serum potassium. In other patients, one or the other effect dominates, and some patients still need a potassium supplement. Initial and periodic determinations of the serum electrolytes to detect a possible electrolyte disturbance should be performed at appropriate intervals.

Thiazides reduce calcium excretion. In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid gland were observed that were accompanied by hypercalcaemia and hypophosphataemia. More severe complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulceration) have not been observed.

Thiazides should be discontinued prior to an examination of parathyroid function.

Thiazides increase the elimination of magnesium in the urine, and hypomagnesaemia may occur (see section 4.5).

Other metabolic disorders
Thiazide diuretics tend to reduce the glucose tolerance and increase the serum level of cholesterol, triglycerides and uric acid. These effects are normally insignificant but in susceptible patients clinically manifest gout or clinically manifest diabetes may occur.

Hyperkalaemia
Concomitant medicinal products that may increase the serum potassium level should be considered carefully. The patients should be made aware that they should use potassium supplements, potassium-containing sodium replacement products or other medicinal products that increase the serum potassium level only after consultation with their physician (see section 4.5).

Hypokalaemia
Conversely, a treatment with thiazide diuretics was associated with the development of hypokalaemia, hyponatraemia and hypochloraemic alkalosis. These types of disorders can manifest themselves in the form of one or several of the following symptoms: dry mouth, thirst, debility, lethargy, sleepiness, restlessness, muscle aches or cramps, muscle weakness, hypotension, oliguria, tachycardia, nausea, confusion, seizures, and vomiting. In addition, hypokalaemia may sensitise or increase the response of

the heart to toxic digitalis effects. At the highest risk for the development of hypokalaemia are patients with cirrhosis of the liver, patients with forced diuresis, patients with insufficient oral ingestion of electrolytes, and patients under concomitant therapy with corticosteroids or ACTH or with other medicinal products that are known to increase the risk of thiazide-diuretics-induced hypokalaemia (see section 4.5).

Diabetes
Thiazide-induced hyperglycaemia can impair blood sugar control. The breakdown of serous potassium increases glucose intolerance. If required, blood sugar control should be monitored and supplementary potassium administered in order to maintain the corresponding serous potassium concentration, and the diabetes medication adjusted if necessary (see section 4.5)

ACE inhibitors may increase sensitivity to insulin in patients with diabetes; they were associated with hypoglycaemia in patients who were treated with oral antidiabetic medicines or insulin. The blood sugar should be monitored carefully, especially during the first month of treatment with an ACE inhibitor (see section 4.5).

Neutropenia/agranulocytosis
ACE inhibitors have rarely been associated with agranulocytosis and bone marrow depression in patients with uncomplicated hypertension; however, more frequently in patients with renal insufficiency, especially if they also suffer from a disease associated with the concomitant ingestion of immunosuppressive medicines or other products that can be associated with neutropenia/agranulocytosis. The patients should be informed that they should report any signs of infection (e.g. throat pain, fever) immediately since these could be the effects of a neutropenia (see section 4.5).

Agranulocytosis has been reported only rarely for a treatment with quinapril. As with other ACE inhibitors leukocyte monitoring should be considered for patients with collagen vascular disorders and/or renal disorders

Surgery/anaesthesiology
For patients who are undergoing major surgery or in case of anaesthesia with active substances that result in hypotension, quinapril may block the angiotensin II formation following the compensatory release of renin. If hypotension occurs and is considered a consequence of this mechanism it can be corrected by volume expansion.

Acute myopia and secondary angle-closure glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain which typically occurs within hours to weeks after the start of the administration of the medicinal product. Untreated angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may be indicated if the intraocular pressure remains uncontrolled. Risk factors for developing angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.
Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC

(see also section 4.8).

Pregnancy
Patients intending to become pregnant should be switched to an alternative antihypertensive treatment which has a suitable safety profile for use during pregnancy. If pregnancy is diagnosed, treatment with Accuzide should be discontinued immediately, and alternative therapy should be started, if needed (see sections 4.3 and 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions between Accuzide, other ACE inhibitors or hydrochlorothiazide were described on concurrent use of:
- Common salt: decrease in antihypertensive effect of Accuzide,
- Antihypertensives (e.g. other diuretics, beta-receptor blockers), nitrates, vasodilators, barbiturates, phenothiazines, tricyclic antidepressants, alcohol: increase of the antihypertensive effect of Accuzide,
- Surgery/anaesthesia: increased drop in blood pressure; in case of emergency surgery pre-anaesthetics and anaesthetics should be administered at reduced dose levels (inform anaesthetist of the therapy with Accuzide).
- Analgesics, non-steroidal antiphlogistic drugs (NSAIDs including COX[cyclooxygenase]-2 inhibitors), antiphlogistics (e.g. salicylic acid derivatives, indomethacin): possible attenuation of the antihypertensive effect of Accuzide (regular monitoring!). NSAID and ACE inhibitors have an additive effect on the increase of the serum potassium concentration and may result in a deterioration of the renal function. Usually, these effects are reversible. Rarely, especially in patients with impaired renal function, such as, for example, dehydrated patients, acute renal failure may occur (regular monitoring!).
- High-dose salicylate administration: increase of toxic CNS effects of salicylates due to hydrochlorothiazide,
- Lithium: elevation of serum lithium concentration (regular monitoring!), thus increase of the cardiotoxic and neurotoxic effect of lithium,
- Alcohol: increase of antihypertensive effect of Accuzide; increased alcohol effect, increase of orthostatic hypotension (also with barbiturates or narcotics),
- Digitalis glycosides: effects and undesirable effects of digitalis glycosides may be increased if a potassium and/or magnesium deficiency exists. Thiazide-induced electrolyte disturbances such as a potassium and/or magnesium deficiency increase the risk of digitalis glycoside toxicity, which can lead to fatal arrhythmia (see section 4.4),
- Medicinal products associated with Torsade de pointes: caution is advised because of the risk of hypokalaemia when using hydrochlorothiazide with medicinal products such as, e.g. digitalis glycosides and other medicinal products that are known to cause Torsade de pointes.
- Oral antidiabetics, insulin: increase of insulin sensitivity and associated hypoglycaemia possible (regular monitoring!; see section 4.4). Thiazide-induced hyperglycaemia can impair blood sugar control. The breakdown of serous potassium increases glucose intolerance. If required, blood sugar control should be monitored and supplementary potassium administered in order to maintain the corresponding serous potassium concentration, and the diabetes medication adjusted if necessary (see section 4.4),
- Catecholamines (e.g. epinephrine, noradrenaline): possible effect attenuation due to hydrochlorothiazide; however not sufficient to rule out its use.
- Kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, carbenoxolone, amphotericin B, penicillin G, salicylates or laxative abuse: increased potassium and/or magnesium loss (especially hypokalaemia) due to hydrochlorothiazide (regular monitoring!),
- Cholestyramine or colestipol: reduced absorption of hydrochlorothiazide from the gastrointestinal tract,

- Allopurinol, cytostatics, immunosuppressants, systemic corticoids, procainamide: decrease in leukocyte count in the blood, leukopenia,
- Cytostatics (e.g. cyclophosphamide, fluorouracil, methotrexate): increased bone marrow toxicity (especially granulocytopenia) due to hydrochlorothiazide,
- Muscle relaxants of the curare type: increase and prolongation of the muscle-relaxing effect of hydrochlorothiazide (inform the anaesthetist of therapy with Accuzide),
- Methyldopa: individual cases of haemolyses due to formation of antibodies to hydrochlorothiazide,
- Neuroleptics, imipramine: increase of the antihypertensive effects of quinapril,
- Tetracycline and other medicinal products that interact with magnesium: during concomitant administration to healthy volunteers a reduced absorption of tetracycline by up to 28 to 37% was determined since the prescription contained magnesium carbonate. Concomitant use with tetracycline should be avoided.
- Antacids: antacids may reduce the bioavailability of quinapril/HCTZ.
- Other active substances: no clinically important pharmacokinetic interactions occurred if quinapril was used concomitantly with propranolol, hydrochlorothiazide or cimetidine.
- Warfarin: the anticoagulant effect (measured with prothrombin time) of an individual dose did not change significantly if quinapril was administered in addition twice daily.

Medicinal products that increase the serum potassium concentration
Concomitant treatment with potassium-sparing diuretics (e.g. spironolactone, amiloride, triamterene), potassium salts as well as other medicinal products that, for their part, may result in a stronger increase of serum potassium concentration (e.g. heparin): stronger increase of serum potassium concentration due to the ACE inhibitor component (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/HCTZ or trimethoprim should therefore be administered with caution concomitantly and the serum potassium concentration should be monitored regularly.

Other drugs known to cause angioedema

Patients simultaneously receiving an mTOR inhibitor (e.g. temsirolimus) or a DPP-4 inhibitor (e.g. vildagliptin) for therapeutic purposes may be at increased risk of angioneurotic oedema. Special care is required if patients already receiving an ACE inhibitor begin a course of treatment with an mTOR inhibitor or a DPP-4 inhibitor.

Clinical trial data has shown that dual blockade of the renin angiotensin aldosterone system (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).
In patients that receive Accuzide and other active substances that affect the renin angiotensin aldosterone system blood pressure, renal function and electrolytes must be closely monitored.

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 use quinapril together with aliskiren for diabetics or patients with impaired renal function (creatinine clearance < 60 ml/min/1.73 m^2).

Medicinal products for the treatment of gout (allopurinol, uricosurics, xanthin-oxigenase inhibitors):
Thiazide-induced hyperuricaemia can impair the treatment of gout with allopurinol or probenecid. The coadministration of hydrochlorothiazide can increase the incidence of hypersensitivity reactions to allopurinol.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of ACE inhibitors and HCTZ is contraindicated during pregnancy (see sections 4.3 and 4.4).

ACE inhibitors
If pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and alternative therapy should be started, if needed.
Treatment with ACE inhibitors during the second and third trimesters of pregnancy is known to induce potential foetotoxic effects (reduced renal function, oligohydramnios, delayed skull ossification) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). , Ultrasound checks of the kidneys and skull are recommended in the case of exposure to ACE inhibitors starting with the second trimester of pregnancy. Infants whose mothers took ACE inhibitors should be monitored repeatedly and closely for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide
Only limited experience is available with the use of hydrochlorothiazide during pregnancy, in particular during the first trimester. Results from animal studies are inadequate.
Hydrochlorothiazide crosses the placenta. Because of the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimesters of pregnancy may result in a foeto-placental perfusion disorder and foetal and neonatal effects such as icterus, electrolyte disturbance and thrombocytopenia.
Because of the risk of reduced plasma volume and placental hypoperfusion without a positive impact on the disease progression, hydrochlorothiazide should not be used in case of gestational oedema or gestational hypertension or pre-eclampsia.

Breastfeeding
A few pharmacokinetic data indicate that very low concentrations of Accuzide are contained in the breast milk (see section 5.2). Even though these concentrations seem to be clinically irrelevant, Accuzide should not be used during breastfeeding of preterm newborn infants as well as during the first weeks after delivery as a potential risk of cardiovascular and renal effects on the infant cannot be ruled out, and no adequate clinical experience for use during lactation is available.

4.7 Effects on ability to drive and use machines

Treatment of hypertension with these medicinal products requires regular medical monitoring. The individually occurring varying reactions may alter the reaction ability to such an extent that the ability of participating in vehicular traffic, operating machinery or working without a safe foothold is reduced. This applies especially at the start of treatment, if the dose is increased and the product changed as well as in conjunction with alcohol consumption.

4.8 Undesirable effects

The following undesirable effects were observed during the treatment with quinapril/HCTZ at the following frequencies:

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)

System organ classes	Frequency	Adverse reactions
Infections and infestations	Common	Viral infections, bronchitis, infections of the upper respiratory tract, pharyngitis[#], rhinitis[#]
	Uncommon	Urinary tract infection, sinusitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Not known	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)^
Blood and lymphatic system disorders	Uncommon	Anaemia, leukopenia, neutropenia[##], eosinophilia[#] (especially in patients with renal impairment, collagen vascular diseases or concomitant treatment with allopurinol, procainamide or certain medicinal products that suppress the defence mechanisms)
	Rare	Haemolytic anaemia[#∞], thrombocytopenia[#]
	Very rare	Agranulocytosis[##], pancytopenia (especially in patients with renal impairment, collagenosis or concomitant treatment with allopurinol, procainamide or certain medicinal products that suppress the defence mechanisms)
Immune system disorders	Rare	Anaphylactoid reaction[#]
Metabolism and nutrition disorders	Common	Hyperkalaemia[##], gout attack[#], hyperuricaemia[#]
	Uncommon	Impaired glucose tolerance
Psychiatric disorders	Common	Insomnia[#] (partly due to disturbance of the water and electrolyte balance)
	Uncommon	Confusion[#], depression[#], nervousness[#], mood changes (partly due to disturbance of the water and electrolyte balance)
Nervous system disorders	Common	Dizziness[#], headaches[#], sleepiness[#], apathy, giddiness (partly due to disturbance of the water and electrolyte balance)
	Uncommon	Transitory ischemic attack[#], syncope[#], paraesthesia[#], taste changes or temporary taste loss (partly due to disturbance of the water and electrolyte balance)[#], balance disorders
Eye disorders	Uncommon	Amblyopia[#], blurred vision[#]; lacrimal liquid formation may be impaired if hydrochlorothiazide is used.
	Not known	Acute myopia and angle-closure glaucoma
Ear and labyrinth disorders	Common	Vertigo[#]
	Uncommon	Tinnitus[#]
Cardiac disorders	Very common	ECG changes and cardiac arrhythmias (caused by hypokalaemia if hydrochlorothiazide is used)
	Common	Angina pectoris[##], tachycardia[#], palpitations[#]
	Uncommon	Myocardial infarction[#]
	Not known	Arrhythmia
Vascular disorders	Common	Vasodilatation[#]

	Uncommon	Especially at the start of Accuzide therapy and in patients with salt and/or fluid deficiency (e.g. in case of vomiting/diarrhoea, pre-treatment with diuretics), severe hypertension, but also if Accuzide dose is increased: hypotension[#] with symptoms such as dizziness, debility, visual disturbances; if high doses of hydrochlorothiazide are used thromboses and embolisms may occur due to haemoconcentrations – especially in elderly patients or if vein disorders are present.
	Very rare	Apoplexy (individual case reports for ACE inhibitors in connection with increased blood pressure drop)
	Not known	Orthostatic hypotension[#]
Respiratory, thoracic and mediastinal disorders	Common	Dry irritant cough, cough[#]
	Uncommon	Dyspnea[#], dry throat
	Rare	Eosinophilic pneumonia[##], obstruction of the upper respiratory tract by angioedema (may be fatal)[#]
	Very rare	Bronchospasms[#], thirst; in isolated cases a sudden onset of pulmonary oedema with shock symptoms has been described; an allergic reaction to hydrochlorothiazide is assumed.
Gastrointestinal disorders	Common	Vomiting[#], diarrhoea[#], digestive disorders[#], upper abdominal discomfort, abdominal pain[#], nausea[#]
	Uncommon	Flatulence[#], dry mouth[#], constipation, loss of appetite
	Rare	Glossitis, pancreatitis[#]
	Very rare	(Sub)ileus[#], intestinal angioedema
Hepatobiliary disorders	Uncommon	Acute cholecystitis (especially in case of pre-existing cholelithiasis)
	Rare	Hepatitis (under ACE inhibitor therapy)[#]
	Very rare	Cholestatic icterus[#], impaired liver function (under ACE inhibitor therapy)
Congenital, familial and genetic disorders	See sections 4.3 and 4.6	
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions such as exanthema[#], urticaria[#], pruritus[#] as well as toxic epidermal necrolysis or angioedema[##] involving lips, face, and/or extremities (very rarely involving larynx, pharynx, and/or tongue [see section 4.9]), alopecia[#], photosensitivity[#], hyperhidrosis[##]
	Rare	Skin disorders may be associated with fever, muscle aches and joint pain (myalgia, arthalgia, arthritis),vasculitis, psoriasiform dermatitis[#], erythema multiforme[#], Stevens Johnson syndrome[#], exfoliative dermatitis[#], pemphigus[#]
	Very rare	Flush, diaphoresis, onycholysis, increase of Raynaud symptoms, cutaneous lupus erythematosus (if hydrochlorothiazide is used); if severe skin reactions are suspected the therapy with Accuzide must be discontinued.

		Note: There is an increased risk of angioedema development in black-skinned patients. In individual cases these skin changes may be accompanied by eosinophilia, leukocytosis, and/or elevated ANA titers, elevated BSR.
	Not known	Purpura
Musculoskeletal, connective tissue and bone disorders	Common	Back pain[#], muscle aches[#]
	Uncommon	Arthralgia[#], muscle cramps, skeletal muscle weakness, pareses (due to hypocalaemia)
	Not known	Systemic lupus erythematosus
Renal and urinary disorders	Common	Impaired renal function may occur or may be intensified[#]
	Uncommon	Proteinuria, sometimes with concurrent deterioration of renal function
	Very rare	Acute renal failure, abacterial interstitial nephritis with consecutive acute renal failure (if hydrochlorothiazide is used)
	Not known	Tubulointerstitial nephritis
Reproductive system and breast disorders	Uncommon	Erectile dysfunction[#]
General disorders and administration site conditions	Common	Fatigue[#], asthenia[#] (partly due to disturbance of the water and electrolyte balance), chest pain[#]
	Uncommon	Generalised oedema[##], fever[#], peripheral oedema[#]
	Not known	Serositis
Investigations	Common	Increase in serum concentrations of urea[#*] and creatinine[#] (especially in patients with impaired renal function), decrease in haemoglobin, haematocrit[#], leukocyte or thrombocyte counts; decrease in sodium concentration in the serum (especially in patients with impaired renal function); the hydrochlorothiazide component may cause hypokalaemia, hypochloraemia, hypomagnesaemia, hypercalcaemia, glucosuria, and metabolic alkalosis.
	Very rare	In individual cases, bilirubin and hepatic enzyme concentrations[#] may be elevated; in isolated cases, haemolysis/haemolytic anaemia also in conjunction with G-6-PDH-deficiency was reported, but a causal relationship with the ACE inhibitor could not be established; elevated levels of blood sugar, cholesterol[#], triglycerides[#], uric acid, amylase in the serum were observed; a serum potassium increase was observed in patients with diabetes mellitus; increased protein excretion in the urine may occur.
	Not known	Antinuclear antibodies increased[#], elevated BSR.

*****These increases appear more likely in patients who receive a concomitant therapy with diuretics than in patients who receive monotherapy with quinapril and often decrease during continued therapy.

^Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-

dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

[#]Undesirable effects that are associated with the quinapril component, frequencies if quinapril/HCTZ is administered.

[##]Undesirable effects that are associated with the quinapril component, frequencies if quinapril is administered. Undesirable effects that are not associated with the quinapril/HCTZ components.

∞In patients with congenital G-6-PDH deficiency, isolated cases of haemolytic anaemia[#] were reported.

Results of clinical laboratory tests
Serum electrolytes: see section 4.4.

Serum uric acid, glucose, magnesium, parathyroid function tests and calcium: see section 4.4.

Haematology test: see section 4.4.

Notes
The above-mentioned laboratory parameters should be monitored before treatment and at regular intervals during treatment with Accuzide. Especially at the start of treatment and in at-risk patients (patients with impaired renal function, collagenosis, treatment with immunosuppressives, cytostatics, allopurinol, procainamide, digitalis glycosides, glucocorticoids, laxatives, elderly patients), serum electrolytes, serum creatinine, blood sugar and blood counts should be closely monitored.

If symptoms such as fever, swollen lymph nodes and/or throat infection occur during therapy with Accuzide, the white blood count must be promptly examined.

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

No specific data on overdosing and the treatment of humans are available for the combination quinapril/HCTZ.

Symptoms of overdosing or intoxication
Depending on the extent of overdosing, the following symptoms may occur: persistent diuresis, electrolyte disturbances, severe hypotension, disturbance of consciousness (as severe as coma), convulsions, pareses, cardiac arrhythmias, bradycardia, circulatory shock, renal failure, paralytic ileus.

Intoxication therapy
a) The following emergency measures are recommended in the event of a life-threatening ***angioedema*** involving the tongue, glottis and/or larynx:

Immediate subcutaneous administration of 0.3-0.5 mg epinephrine (e.g. 0.3–0.5 mL of a 1:1,000 solution) or ***slow*** intravenous administration of 0.1 mg epinephrine (follow the dilution instructions!) under ECG and blood pressure monitoring followed by systemic glucocorticoid administration.

In addition, intravenous administration of antihistamines and H_2-receptor antagonists is recommended.

In addition to epinephrine administration, the administration of C_1-inactivator can be considered with known C_1-inactivator deficiency.

b) Therapeutic measures in the case of overdosing or intoxication depend on the mode and time of administration and the type and severity of the symptoms. In addition to general measures to eliminate Accuzide (e.g. gastric lavage, administration of adsorbents and sodium sulfate within 30 minutes after ingestion of Accuzide), the vital parameters must be monitored or adjusted under intensive care medical conditions. Quinapril and hydrochlorothiazide cannot be quantitatively dialysed.

In cases of hypotension, a common salt and volume substitution should initially take place; if the response is not adequate, catecholamines should be administered intravenously in addition. Therapy with angiotensin II can be considered.

Pacemaker therapy is indicated in the case of therapy-resistant bradycardia.

Water, electrolyte and acid-base balances and blood sugar and substances eliminated with urine must be closely monitored. Potassium substitution is required in the event of hypokalaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combination of angiotensin-converting-enzyme-inhibitor and thiazide diuretic, ATC code: C09BA06

Accuzide has both antihypertensive and diuretic effects.

Quinapril and hydrochlorothiazide are used alone and in combination for the treatment of hypertension. The antihypertensive effects of the two components are approximately additive. Quinapril can reduce the potassium loss associated with hydrochlorothiazide.

Mechanism of action

Quinapril
Quinapril is hydrolysed in the liver to quinaprilat, which is an inhibitor of the angiotensin-converting-enzyme (ACE). The angiotensin-converting-enzyme is a peptidyldipeptidase that effects the conversion of angiotensin I to the active vasoconstricting substance angiotensin II. Inhibition of ACE results in reduced formation of v angiotensin II that has a vasoconstrictive effect in tissues and plasma, resulting in a decrease of aldosterone secretion and consequently an increase in serum potassium concentration. Increase of the plasma-renin activity results from the discontinuation of the negative back-coupling of angiotensin II to the renin secretion.

Since ACE also metabolises bradykinin, a vasodepressive peptide, increased activity of the circulating and local kallikrein-kinin systems (and thus an activation of the prostaglandin system) results from the ACE inhibition. . It is possible that this mechanism plays a role in the blood-pressure reducing effect of the ACE inhibitors and certain undesirable effects.

Hydrochlorothiazide
Hydrochlorothiazide is a benzothiadiazine. Thiazides act directly on the kidneys by increasing sodium chloride and associated water excretion. The early-distal tubulus is the clinically relevant main site of attack. There, they inhibit electroneutral NaCl-co-transport in the luminal cell membrane. Potassium and magnesium excretion is increased, and calcium excretion reduced. Hydrochlorothiazide effects a low hydrogen carbonate excretion, and the chloride excretion exceeds the sodium excretion. Metabolic alkalosis may develop if hydrochlorothiazide is used. Hydrochlorothiazide is actively secreted in the proximal tubule. The diuretic effect is maintained for metabolic acidosis or metabolic alkalosis.

Changes in sodium balance, a reduction of the extracellular water and plasma volume, a change in

renal vascular resistance and a reduced responsiveness to norepinephrine and angiotensin II are discussed as mechanisms of the antihypertensive effect of hydrochlorothiazide.

Pharmacodynamics

Quinapril

In hypertensive patients, quinapril reduces the blood pressure in the supine and standing positions without a compensatory increase of the heart rate.

In haemodynamic studies, quinapril effected a marked reduction of peripheral arterial resistance. Usually, there were no clinically relevant changes in renal plasma flow and glomerular filtration rate.

In most patients, the onset of the antihypertensive effect was observed approx. 1 hour after oral administration of Accuzide, and the maximum effect was achieved usually after approx. 2-4 hours. The maximum hypotensive effect of a defined quinapril dose was usually apparent after 3-4 weeks.

At the recommended daily dose, the antihypertensive effect is maintained even during long-term therapy. Abrupt discontinuation of Accuzide does not result in a rapid, excessive increase in blood pressure (rebound).

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 with 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.

Hydrochlorothiazide

The electrolyte and water excretion of hydrochlorothiazide starts 2 hours after administration; it reaches the maximum effect after 3-6 hours and lasts for 6-12 hours.

The antihypertensive effect starts only after 3-4 days and may last up to one week after the end of therapy.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥ 50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls,

using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Quinapril
Maximum quinapril concentrations are found within 1 hour following oral administration of quinapril. Food intake does not affect the absorption of quinapril. After absorption, quinapril is rapidly and almost completely metabolised to the actually active main metabolite quinaprilat. In addition, a few other quantitatively unimportant and pharmacologically inactive metabolites occur. Maximum plasma levels of quinaprilat, the effective metabolite, are observed approx. 2-3 hours after oral administration of quinapril. The protein binding of quinapril and quinaprilat is approx. 97%. Approx. 60% of a quinapril dose is eliminated renally, and 40% with the faeces. Quinaprilat is eliminated primarily via the kidneys, the effective accumulation half-life is approx. 3 hours, the dissociation half-life of ACE approx. 26 hours. Normal quinapril and quinaprilat plasma level progressions were found in patients with renal insufficiency up to a creatinine clearance of 60 mL/min. At a creatinine clearance of less than 60 mL/min, the quinaprilat levels increase, the time until the maximum plasma level is reached is prolonged, and the elimination half-life is also prolonged.

Pharmacokinetic studies on patients with terminal kidney diseases, who are chronically haemodialysed or were treated with outpatient peritoneal dialysis showed that dialysis has only a slight effect on the elimination of quinapril and quinaprilat.

The elimination of quinaprilat is also slower in elderly patients (older than 65 years) and in patients with severe cardiac failure; the slowed down elimination correlates with a renal function impairment that is often present in elderly patients. It may therefore be necessary to reduce the quinapril dose in patients with moderately impaired renal function (creatinine clearance: 30-60 mL/min) and in elderly patients. Reduced quinaprilat plasma levels were measured in patients with liver cirrhosis, which can be attributed to a reduced metabolisation of quinapril in its passage through the liver.

Hydrochlorothiazide
Hydrochlorothiazide is absorbed 60-80% after oral administration. Peak plasma concentrations of hydrochlorothiazide in the amount of 70 ng/mL were reached 1.5-4 hours after oral administration of 12.5 mg hydrochlorothiazide; of 142 ng/mL 2-5 hours after 25 mg hydrochlorothiazide p.o.; and of 260 ng/mL 2-4 hours after 50 mg hydrochlorothiazide p.o.

65% of hydrochlorothiazide is bound to plasma proteins; the relative distribution volume is 0.5-1.1 L/kg.

Hydrochlorothiazide is excreted almost completely unchanged via the kidneys (more than 95%), after an oral single dose, 50-70% of the dose is excreted within 24 hours, and detectable quantities are found in the urine already after 60 minutes.

The elimination half-life is 6-8 hours.
A decreased excretion and prolongation of the half-life are observed in the case of kidney failure. In the process, the renal clearance of hydrochlorothiazide shows a close correlation with the creatinine clearance.

There is no relevant change in the pharmacokinetics of hydrochlorothiazide in the case of liver cirrhosis. No studies on hydrochlorothiazide kinetics are available for patients with cardiac failure.

Bioavailability
Quinapril
Based on recovery studies in the urine, the extent of absorption of quinapril after oral administration is approx. 60%.

Following the oral administration of a single dose of 20 mg quinapril to 6 breast-feeding women, the milk/plasma (M/P ratio) ratio for quinapril was 0.12. Four hours after administration no quinapril was found in the breast milk. The quinaprilat concentrations in the breast milk were below the detection limits (<5 µg/L) at all times. It has been estimated that a breast-fed infant would ingest approximately 1.6% of the quinapril dose given to the mother.

Hydrochlorothiazide
The bioavailability of hydrochlorothiazide is approx. 70% after oral administration.

Combined administration of quinapril and hydrochlorothiazide
Accuzide film-coated tablets are bioequivalent with the concurrent administration of the respective individual substances.

5.3 Preclinical safety data

Quinapril
Acute toxicity
The LD_{50} values following oral administration of quinapril were 1,440-2,150 mg/kg BW in mice and 3,541-4,280 mg/kg BW in rats. After intravenous administration, the values were 504-523 mg/kg BW (mice) and 107-300 mg/kg BW (rats).

Chronic toxicity
Chronic toxicity was tested in rats and dogs at doses of up to 100 mg/kg BW over a period of 1 year. Weight loss, an increase in BUN and renin, and a decrease in glucose values were observed. Heart weights were reduced, kidneys showed degenerative changes and juxtaglomerular hypertrophy or hyperplasia. Similar results were found in studies with dogs. In this case, an increase in plasma-renin values and a juxtaglomerular hypertrophy were also observed. BUN and hepatic enzyme values were elevated in a few animals at the highest dose.
A few animals developed gastric erosions; focal inflammations of the liver were observed in the highest dose group. The renal changes observed in rats and dogs at very high doses are typical of ACE inhibitors and do not appear to be due to a direct toxic effect, but rather to excessive pharmacological effects (markedly prolonged blood pressure reduction, stimulation of cells containing renin).

Tumorigenic and mutagenic potential
No tumorigenic effects were observed in studies on rats and mice that received daily doses of 75 and 100 mg/kg BW, respectively.

Quinapril was found to have no mutagenic effects in an adequate investigation of gene and chromosome mutation tests *in vitro* and *in vivo*.

Reproduction toxicity
Studies with doses up to 300 mg/kg BW/day in rats and 1.5 mg/kg BW/day in rabbits, respectively, revealed no evidence of a teratogenic potential. Whereas no embryotoxic effects were observed in rats, maternal-toxic and embryotoxic effects occurred in rabbits starting at a dose of 1 mg/kg BW/day. If administered during foetal development and lactation, doses starting at 25 mg/kg BW/day in rats resulted in retarded growth of the offspring. No impairment of fertility was observed in either parent or offspring animals.

Hydrochlorothiazide
Acute toxicity
Animal experimental studies on acute toxicity in mice showed an LD_{50} greater than 10,000 mg/kg BW after oral administration of the suspension and of 884 mg/kg BW after intravenous administration. In rats, the acute LD_{50} was greater than 10,000 mg/kg BW after oral administration of the suspension and 3,130 mg/kg BW after intraperitoneal administration of the suspension. In rabbits, the acute LD_{50} after intravenous administration was 461 mg/kg BW, and in dogs it was approximately 1,000 mg/kg BW.

Dogs tolerated at least 2,000 mg/kg BW without signs of toxicity.

Subchronic and chronic toxicity
There were no marked findings in studies on subchronic and chronic toxicity in rats and dogs except changes in the electrolyte balance.

Carcinogenicity
Hydrochlorothiazide was administered with feed for 2 years to male and female rats at concentrations of up to 2,000 ppm and to male and female mice at concentrations of up to 5,000 ppm. No carcinogenic effect was observed in male and female rats and in female mice. In male mice, an increased occurrence of hepatic cell tumours was observed, but the relevance with respect to a possible carcinogenicity is questionable.

Mutagenicity
Hydrochlorothiazide showed no relevant mutagenic effects in an adequate *in vitro* and *in vivo* investigation.

Reproduction toxicity
Hydrochlorothiazide passes the placental barrier in the animal experiment. Studies on three animal species (rats, mice, rabbits) showed no evidence of a teratogenic effect.
Experience in humans is available with the use during pregnancy in more than 7,500 mother-child pairs. 107 of them were exposed during the first trimester. It is suspected that thrombocytopenia may be triggered in newborn infants. Effects of disturbances of the electrolyte balance in the pregnant woman on the foetus are possible.
Low quantities of hydrochlorothiazide pass into the breast milk. It is known that thiazide diuretics may inhibit lactation.

Toxicological properties of the combination of quinapril and hydrochlorothiazide
Acute toxicity
The LD_{50} after oral administration of the combination quinapril/hydrochlorothiazide was 1,073 mg/kg BW quinapril/669 mg/kg BW hydrochlorothiazide in female mice. The acute toxicity of the combination does not differ significantly from that of the monosubstance quinapril.

Subchronic toxicity
Repeated administration of quinapril/hydrochlorothiazide to rats and dogs showed no other unexpected toxic effects than if the two active substances were administered separately. The frequency of the expected renal and gastrointestinal effects was, however, higher following the administration of the combination than after the administration of quinapril alone.

These toxic effects of the combined administration of quinapril and hydrochlorothiazide are not to be expected after therapeutic use.

Carcinogenicity and mutagenicity
No studies were performed with the combination.

Reproduction toxicity
Administration of the combination quinapril/hydrochlorothiazide to rats between the 6th and 15th day of gestation resulted in the death of the dam in 2 of 20 animals at a dose of 150/93.8 mg/kg BW/day. At doses of more than 50/31.3 mg/kg BW/day, the maternal weight gain was reduced. The mean body weight of female rat foetuses was reduced starting at a dose of 5/3.1 mg/kg BW/day. This weight reduction occurred in foetuses of both sexes starting at a ten times higher dose.

There were no deaths following administration of the combination at doses of 0.05/0.03 mg/kg BW/day to 0.5/0.31 mg/kg BW/day to rabbits between the 6th and 18th day of gestation. However, weight loss was observed in the dams in all dose groups.
No studies are available on the passage into the breast milk or the transfer to the placenta.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Candelilla wax, crospovidone, hyprolose, lactose monohydrate, macrogol 400, heavy basic magnesium carbonate, magnesium stearate (Ph.Eur.), hypromellose, povidone K 25, titanium dioxide (E171), iron oxide hydrate (E172), iron(III)-oxide (E172)

6.2 Incompatibilities

Incompatibilities are not known so far.

6.3 Shelf life

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

6.4 Special precautions for storage

Keep out of the sight and reach of children.

Store in a cool dry place not exceeding 25 °C

6.5 Nature and contents of container

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

Accuzide 20 mg/12.5 mg:
30 film-coated tablets (N1)
100 film-coated tablets (N3)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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.

No special requirements.

7. FURTHER INFORMATION

Marketing Authorization Holder

Pfizer Pharma PFE GmbH
Linkstr. 10
10785 Berlin
Federal Republic of Germany

Manufacturer (Bulk, Packager, Batch Releaser)

Pfizer Manufacturing Deutschland GMBH Betriebsstätte Freiburg ,
Mooswaldallee 1
79090 Freiburg
Federal Republic of Germany

8. DATE OF REVISION OF THE TEXT

November 2018

9. SALES RESTRICTIONS

Available only on prescription

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