Accuzide® 20

1.Description of Drug
Accuzide® 20
2.Composition of Drug
2.1Category of Substance or Indication
Combination of angiotensin-converting-enzyme-inhibitor and thiazide diuretic, antihypertensive
2.2 Medicinally Active Ingredients
Accuzide 20
1 film-coated tablet contains:
21.664 mg of quinapril hydrochloride (corresponding to 20 mg of quinapril),12.50 mg of hydrochlorothiazide
2.3 Other Ingredients
Candelilla wax, crospovidone, hydroxypropyl cellulose, lactose 1 H_2O, macrogol 400, heavy basic magnesium carbonate, magnesium stearate, methylhydroxypropyl cellulose, povidone, cf. yes E 171, E 172
3.Indications
Essential hypertension. Accuzide film-coated tablets are indicated in patients whose hypertension could not adequately be lowered with quinapril alone.
4.Contraindications
Accuzide should not be used in:
– Hypersensitivity to quinapril hydrochloride, thiazides or sulfonamides (bear in mind possible cross reactions)
– Known history of angioneurotic edema (e.g. as a result of previous ACE-inhibitor therapy)
– Serious impairment of renal function (serum creatinine more than 1.8 mg/dl or creatinine clearance less than 30 ml/min)
– Dialysis patients
– Stenosis of the renal arteries (bilateral or in single kidney)
– Status after kidney transplantation
– Hemodynamically relevant aortic or mitral valve stenosis or hypertrophic cardiomyopathy
– Decompensated heart failure
– Primary hyperaldosteronism
– Serious impairment of hepatic function (precoma/coma hepaticum) or primary hepatic disease
– Clinically relevant electrolyte imbalance (hypercalcemia, hyponatremia, hypokalemia)
– Children (due to a lack of therapeutic experience)
Life-threatening hypersensitivity reactions may occur during LDL (low-density lipoprotein)-apheresis (in serious hypercholesterinemia) with dextrane sulfate and concurrent administration of an ACE inhibitor.
Sometimes life-threatening hypersensitivity reactions (e.g. blood pressure fall, dyspnea, vomiting, allergic skin reactions) may occur during treatment to reduce or cancel the allergic reaction threshold (desensitization therapy) for insect toxins (such as bee or wasp sting) and concurrent administration of an ACE inhibitor.
If LDL apheresis or desensitization therapy against insect toxins is necessary, the preparation must be temporarily replaced by other antihypertensive drugs.
During treatment with Accuzide no dialysis or hemofiltration with polyacrylnitril-methallylsulfonate-high-flux membranes (e.g. "AN 69") may be made, since there is the risk during dialysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) up to life-threatening shock may occur. In case of emergency dialysis or hemofiltration, a switch must therefore be made to another antihypertensive – no ACE inhibitor - or a different dialysis membrane should be used. Pregnancy must be ruled out in women of childbearing potential before using an ACE inhibitor combination like Accuzide. These women must use adequate contraception during treatment with Accuzide. If pregnancy is determined during treatment with Accuzide, a switch must be made under medical supervision to a different possible therapy with less risk for the child, since damage to the child may occur if Accuzide is taken especially during the last 6 months of pregnancy. Breastfeeding is to be stopped if treatment during lactation is required.
Accuzide 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:
- clinically relevant proteinuria (more than 1 g/day)
- impaired immunoreaction or collagen disease (e.g. lupus erythematodes, scleroderma)
- concurrent systemic therapy with drugs which suppress the defense reactions (e.g. corticoids, cytostatics, antimetabolites), allopurinol, procainamide or lithium
- gout
- hypovolemia
- cerebral sclerosis
- coronary sclerosis
- manifest or latent diabetes mellitus
- impaired hepatic function

Notes (see also section Dosing)
Renal function must be checked prior to administration of Accuzide. A salt/fluid deficiency must be balanced prior to beginning therapy.
Especially at the start of therapy Accuzide should be used only under intensive monitoring of blood pressure 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

Corresponding to the application options of the individual substances, Accuzide may be administered in those cases of reduced cardiac performance, in which the dose of the individual substances was previously reached, which corresponds to the composition of Accuzide.
5. Adverse Reactions
The following adverse reactions were observed during therapy with Accuzide or other ACE inhibitors or hydrochlorothiazide:
Cardiovascular system
Occasionally, especially at the start of Accuzide therapy, and in patients with salt and/or fluid deficiency (e.g. vomiting/diar rhea, previous diuretic treatment), serious hypertension or also if the dose of Accuzide is increased, excessive reduction of blood pressure (hypotension, orthostasis with symptoms like dizziness, feeling of weakness, blurred vision, rarely loss of consciousness (syncope) may occur.
ECG changes and cardiac arrhythmias may result frequently during hydrochlorothiazide.Isolated cases of the following adverse reactions were reported in connection with ACE inhibitors in association with a potentiated decrease in blood pressure: Tachycardia, palpitations, chest pain, angina pectoris, myocardial infarction, TIA, cerebral hemorrhage.
Kidneys
Occasionally, impairments of renal function may occur or worsen, in isolated cases up to acute kidney failure. Proteinuria, sometimes with concurrent deterioration of renal function, was observed in rare cases. Isolated cases of abacterial interstitial nephritis with consecutive acute renal failure were reported under hydrochlorothiazide.
Respiratory tract
Occasionally, dry irritative cough and bronchitis, rarely dyspnea, sinusitis, rhinitis, in isolated cases bronchospasms, glossitis, dry mouth and thirst may occur. In isolated cases, a sudden onset of pulmonary edema with shock symptoms was described. An allergic reaction to hydrochlorothiazide is assumed. Angioneurotic edema induced by ACE inhibitors involved in isolated cases larynx, throat and/or tongue (see section 12 Emergency measures).
Note: There is an increased risk of angioneurotic edema in black patients.
Gastrointestinal tract/Liver
Occasionally, nausea, upper abdominal discomfort, indigestion, rarely vomiting, diarrhea, constipation, anorexia, pancreatitis and - especially with pre-existing cholelithiasis - acute cholecystitis may occur. Individual cases of cholestatic icterus, impaired liver function, hepatitis and (sub) ileus were described under ACE inhibitor therapy.
Skin, Vascular system
Occasionally allergic skin reactions like exanthema, rarely urticaria, pruritus or skin reactions like pemphigus, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, cutaneous lupus erythematodes (isolated cases under hydrochlorothiazide) and toxic epidermal necrolysis or angioneurotic edema involving lips, face and/or extremities may occur. These skin changes may be accompanied in some cases by fever, myalgias, arthralgias/arthritis, vasculitis, eosinophilia, leukocytosis and/or elevated ANA titers, elevated ESR. Thromboses and embolisms may occur rarely under high doses of hydrochlorothiazide due to hemoconcentrations - especially in elderly patients or in the presence of venous diseases. Impaired tear secretion occurred in rare cases under hydrochlorothiazide.
Nervous system
Occasionally, due in part to imbalances in water and electrolytes - headache, fatigue, somnolence, weakness, apathy, rarely dep ressions, giddiness, insomnia, impotence, paresthesias, dysequilibrium, confusion, changes in mood, tinnitus, blurred vision and changes in the sense of taste or transient loss of the sense of taste may occur.
Locomotor system
Muscle cramps, weakness of skeletal muscles, muscle pain, gout attack and, due to hypokalemia, pareses may occur in rare cases.
Laboratory parameters
Occasionally, there is a decrease in hemoglobin, hematocrit, leukocyte or thrombocyte counts.
Rarely especially in patients with impaired renal function, collagen diseases or concurrent therapy with allopurinol, procainamide or certain drugs which suppress the defense reactions, anemia, thrombocytopenia, leukopenia, neutropenia, eosinophilia, in isolated cases agranulocytosis or pancytopenia may occur.
Hemolysis/hemolytic anemia also in conjunction with G-6-PDH-deficiency was reported in isolated cases, but a causal relationship to the ACE inhibitor could not be substantiated.

The ingredient hydrochlorothiazide may occasionally induce hypokalemia, hypochloremia, hypomagnesiemia, hypercalcemia, glucosuria and metabolic alkalosis. Elevations of blood sugar, cholesterol, triglycerides, uric acid, amylase in the serum were observed.
Occasionally, especially in patients with impaired renal function, serum concentrations of urea, creatinine and potassium may increase and sodium concentration in the serum may decrease. Increased protein excretion in the urine may occur. In individual cases, bilirubin and hepatic enzyme concentrations may increase.
Notes: The above mentioned laboratory parameters should be monitored before and at regular intervals during treatment with Accuzide. Especially at the start of treatment and in risk patients (patients with impaired renal function, collagen diseases, treatment with immunosuppressives, cytostatics, allopurinol, procainamide, digitalis glycosides, glucocorticoids laxatives, elderly patients), monitoring of serum electrolytes, serum creatinine, blood sugar and blood counts should be performed at short intervals. If symptoms like fever, swollen lymph nodes and/or inflamed throat should occur during therapy with Accuzide, the white blood count must be examined without delay.
Note for participants in vehicular traffic:
Treatment of hypertension with this medication requires regular medical control. The individually varying reactions may alter the reaction capacity to such an extent that the capability of participating in vehicular traffic, operating machinery or working without a safe toothold is reduced. This applies especially at the start of treatment, if the dose is increased and upon change of preparations, as well as in conjunction with alcohol.
6. Drug Interactions
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: Potentiation of the antihypertensive effect of Accuzide
- Analgesics, antiphlogistics (e.g. salicylic acid derivatives, indomethacin): Possible weakening of the antihypertensive effect of Accuzide. Acute renal failure may be induced, especially in hypovolemia
- High-dose salicylate administration: Potentiation of toxic CNS effects of salicylates due to hydrochlorothiazide
- Potassium, potassium-sparing diuretics (e.g. spironolactone, amiloride, triamteren) and other drugs which, for their part, may result in a stronger increase in serum potassium concentration (e.g. heparin): Stronger increase in serum potassium concentration due to ACE inhibitor component.
- Lithium: Elevation of serum lithium concentration (regular control), thus potentiation of the cardiotoxic and neurotoxic effect of lithium
- Alcohol: Potentiation of antihypertensive effect of Accuzide; potentiated alcohol effect
- Digitalis glycosides: Effects and side effects of digitalis glycosides may be potentiated in the presence of potassium and/or magnesium deficiency.
- Oral hypoglycemics, insulin: Decreased effect due to hydrochlorothiazide
- Catecholamines (e.g. epinephrine): Reduction of effect due to hydrochlorothiazide
- Kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, carbenoxolon, amphotericin B, penicillin G, salicylates or laxative abuse: Increased potassium and/or magnesium loss due to hydrochlorothiazide
- Cholestyramine or colestipol: Reduced absorption of hydrochlorothiazide
- 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
- Narcotics, anesthetics: Stronger blood pressure fall (inform the anesthetist about therapy with Accuzide)
- Muscle relaxants of the curare type: Potentiation and prolongation of the muscle-relaxing effect due to hydrochlorothiazide (inform the anesthetist about therapy with Accuzide)
- Methyldopa: Individual cases of hemolysis due to formation of antibodies to hydrochlorothiazide
- Neuroleptics, imipramin: Potentiation of the antihypertensive effects of quinapril
- Tetracyclines: Reduced absorption of tetracyclines

7. Warnings
Accuzide should not be used with polyacrylnitril-methallylsulfonate-high-flux membranes (e.g. AN 69), during LDL-apheresis with dextrane sulfate or during desensitization treatment to insect toxins (see point 5 Contraindications).
8. Most Important Incompatibilities
Incompatibilities are unknown so far.
9. Dosage including Single and Daily Doses
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 hydrochloride and hydrochlorothiazide). If clinically appropriate, direct change from monotherapy to the 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. vomiting/diarrhea, prior diuretic treatment), severe hypertension - these patients must be monitored for at least 6 hours.
Dosage 20
The usual daily dose for patients in whom a combination therapy is indicated is 1 film-coated tablet Accuzide 20 (corresponding to 20 mg quinapril and 12.5 mg hydrochlorothiazide) in the morning. A dose of 1 film-coated tablet Accuzide per day should not be exceeded.
Dosage in moderately impaired renal function (creatinine clearance 30-60 ml/min or serum creatinine concentration 1.2-1.8 mg/dl) 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 failure (creatinine excretion 30-60 ml/min) should be started with 5 mg quinapril as monotherapy and titrated to the appropriate dose level (not above 20 mg quinapril). Dose titration with hydrochlorothiazide may follow for patients who additionally require a diuretic. Patients with serious renal failure (creatinine clearance less than 30 ml/min) are to be excluded from treatment with Accuzide.
10. Dosage and Duration of Administration
Accuzide can be taken independent of meals. The individual daily quantity should be swallowed whole with sufficient fluid in a single dose in the morning. The physician determines the duration of administration.
11. Emergency Measures, Symptoms and Antidotes
11.1 Symptoms of overdosing or toxic effects
Depending on the extent of overdosing, the following symptoms may occur: Persistent diuresis, electrolyte imbalance, serious hypotension, disturbance of consciousness (up to coma), convulsions, pareses, cardiac arrhythmias, bradycardia, cardiovascular shock, renal failure, paralytic ileus.
11.2 Therapy of toxic effects
a) The following emergency measures are recommended in the advent of angioneurotic edema involving tongue, glottis and/or larynx:
Immediate subcutaneous administration of 0.3-0.5 mg epinephrine or slow intravenous administration of 0.1 mg epinephrine (follow the dilution instructions!) under ECG and blood pressure monitoring, then systemic glucocorticoid administration. Furthermore, intravenous administration of antihistamines and H2-receptor antagonists is recommended.
In addition to epinephrine administration, if C1-inactivator deficiency is known, administration of C1-inactivator should be considered.
b) Therapeutic measures in case of overdose or toxic effects depend on the mode and time of administration and the nature and seriousness of symptoms. In addition to general measures to support Accuzide elimination, (e.g. gastric lavage, administration of absorbents and sodium sulfate within 30 minutes after ingestion of Accuzide), the vital parameters must be monitored or corrected under intensive medical conditions. Quinapril and hydrochlorothiazide cannot be quantitatively dialyzed. In cases of hypotension, saline and volume substitution should first be initiated if the respective contraindications do not exist. Additional catecholamines should be administered intravenously. Therapy with angiotensin II should be considered. Placental transfer therapy is indicated in therapy-resistant bradycardia.
Monitoring of water, electrolyte and acid-base balances and of blood sugar and substances eliminated with urine must be continuously performed. Potassium substitution is required in the event of hypokalemia.
12. Pharmacological and Toxicological Properties
12.1 Pharmacological Properties
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 both components are additive. Quinapril can reduce the potassium loss associated with hydrochlorothiazide.
Mechanism of action
- *Quinapril*

Quinapril is hydrolyzed in the liver to quinaprilat, which is an angiotensin-converting-enzyme inhibitor. The angiotensin-converting-enzyme (ACE) is a peptidyldipeptidase, which mediates the conversion of Angiotensin I to the vasoconstrictive active substance angiotensin II. Inhibition of ACE results in reduction of the vasoconstrictive effect of angiotensin II in tissues and ACE mediated aldosterone secretion and thus an increase in serum potassium concentration. Elevation of plasma-renin activity which results from the cancellation of the negative back-coupling of angiotensin II to renin secretion.Since ACE also metabolizes bradykinin, a vasodepressive peptide, inhibition of ACE also results in elevated activity of the circulating and local kallikrein-kinin systems (and thus in activation of the prostaglandin system). It is possible that this mechanism is involved in the blood-pressure reducing effect of the ACE inhibitor and is co-responsible for certain adverse reactions.
- *Hydrochlorothiazide*

Hydrochlorothiazide is a benzothiadiazide. Thiazides act directly on the kidneys by increasing sodium chloride and the associated water excretion. The early-distal tubulus is the main site of clinically relevant action. There, they inhibit electroneutral NaCl-cotransport in the luminal cell membrane. Potassium and magnesium excretion is increased, calcium excretion reduced. Hydrochlorothiazide produces low hydrogen carbonate excretion, and the chloride excretion exceeds sodium excretion. Metabo-lic alkalosis may develop under hydrochlorothiazide. Hydrochlorothiazide is actively broken down in the proximal tubulus. The diuretic effect is maintained in metabolic acidosis or metabolic alkalosis.
Changes in sodium balance. reduction of extracellular water and plasma volume, change in renal vascular resistance and reduced responsiveness to norepinephrine and angiotensin II are discussed as mechanisms of the antihypertensive effect of hydrochlorothiazide.
Pharmacodynamics
- *Quinapril*

In hypertensive patients, quinapril leads to a reduction of blood pressure both in the supine and standing positions, without a compensatory increase in heart rate.
In hemodynamic studies, quinapril produced a marked reduction of peripheral arterial ill 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 approx. 1 hour after oral administration of Accuzide, 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.
With the recommended daily dose, the antihypertensive effect is maintained even during long-term therapy. Abrupt withdrawal of Accuzide does not result in a rapid, excessive increase in blood pressure (rebound).
- *Hydrochlorothiazide*

The onset of electrolyte and water excretion of hydrochlorothiazide starts 2 hours after administration, reaches the maximum effect after 3-6 hours and lasts for 6-12 hours.
The onset of antihypertensive effect is after 3-4 days and may last up to one week after the end of therapy.
12.2 Toxicological Properties
- *Quinapril*

Acute toxicity
The LD_{50} values following oral administration of quinapril were 1440-2150 mg/kg BW in mice and 3541-4280 mg/kg BW in rats. After intravenous administration, 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 with doses up to 100 mg/kg BW over a period of 1 year. Weight loss, increase in BUN, renin and decrease in glucose values were observed. Heart weights were reduced, kidneys showed degenerative changes and juxtaglomerular hypertrophy or hyperplasia. A similar pattern was found in studies with dogs. Here, there was also an elevation in plasma-renin values and juxtaglomerular hypertrophy. BUN and hepatic enzyme values were elevated in some of the animals at the highest dose. Some animals developed gastric erosions, focal inflammations of the liver were observed in the highest dose group. The renal changes observed in rats and dogs under 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 of rats and mice with daily doses of 75 and 100 mg/kg BW, respectively.
Quinapril was not mutagenic in adequate investigations 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. Quinapril gene and chromosome mutation tests in vitro and in vivo, 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.
No studies of placental penetration and appearance in breast milk are known. Experience is inadequate concerning the safety of use of ACE inhibitors during pregnancy in humans. Cases of fetal syndrome have been reported in the past few years, characterized by serious hypoplasia of skull bones, retardation of intrauterine growth, oligohydramnia and neonatal anuria, which may result in the death of the neonate. The hypotensive effect on the fetus during the second and third trimester of pregnancy is assumed to be the cause. Such effects are not to be expected if therapy is switched in time to other antihypertensive drugs in the first trimester of pregnancy.No experience is known concerning the use during lactation in humans.
- *Hydrochlorothiazide*

Acute Toxicity
Animal experimental acute toxicity studies in mice showed an LD50 greater than 10 000 mg/kg BW after oral administration of the suspension and 884 mg/kg BW after intravenous administration. In rats, the acute LD50 was greater than 10 000 mg/kg BW after oral administration of the suspension and 3130 mg/kg BW after intravenous administration of the suspension. In rabbits, the acute LD50 after intravenous administration was 461 mg/kg BW, and in dogs, it was about 1000 mg/kg BW. Dogs tolerated at least 2000 mg/kg BW without signs of toxicity.
Subchronic and chronic toxicity There were no striking findings in studies of subchronic and chronic toxicity in rats and dogs except for changes in the electrolyte balance.
Carcinogenicity
Hydrochlorothiazide was administered for 2 years to male and female rats at concentrations of up to 2000 ppm and to male and female mice at concentrations of up to 5000 ppm with feed. No carcinogenic effect was observed in male and female rats, or in female mice. In male mice, an increased occurrence of hepatic cell tumors was observed, but the relevance with respect to a possible carcinogenicity is doubtful. Mutagenicity hydrochlorothiazide showed no relevant mutagenic effects in a sufficient in vitro and in vivo investigation.
Reproduction toxicity
Hydrochlorothiazide passes the placental barrier in animal experiments. Studies in 3 animal species (rats, mice, rabbits) showed no evidence of a teratogenic effect.
Experience in humans is available with the use during pregnancy in over 7500 mother-child pairs.Thereof, 107 were exposed in the first trimester. There is the suspicion that thrombocytopenia may be provoked in the neonate. Effects of electrolyte imbalance on the fetus in the pregnant woman are possible. Low quantities of hydrochlorothiazide appear in breast milk. It is known that thiazide diuretics may inhibit lactation.
- Toxicological properties of the combination of quinapril and hydrochlorothiazide Acute Toxicity

The LD50 after oral administration of the combination quinapril/hydrochlorothiazide was 1073 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 when the two active substances were administered separately.The frequency of the expected renal and gastrointestinal effects were, however, higher following the combination than after quinapril alone.
These toxic effects of the combined administration of quinapril and hydrochlorothiazide are not to be expected after therapeutic applications.
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 mater nal weight gain was reduced. The mean body weight of female rat fetuses was reduced at doses starting with 50.1 mg/kg BW/day This weight reduction occurred in fetuses at ten times higher doses. There were no deaths following administration of the combination in 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 were performed on the appearance in breast milk or on peri- and postnatal effects.
12.3 Pharmacokinetics
- *Quinapril*

Maximum quinaprilat concentrations are found within 1 hour following oral administration of quinapril. Food intake has no influence on the absorption of quinapril. After absorption, quinapril is rapidly and almost completely metabolized to the active main metabolite quinaprilat. In addition, some other, quantitatively unimportant pharmacologically inactive metabolites are produced. Maximum plasma levels of quinaprilat, the active metabolite, are observed approx. 2-3 h after oral administration of quinapril. Protein binding of quinapril and quinaprilat is approx. 97 %. Approx. 60 % of a quinaprilat dose are eliminated renally, 40 % with the feces. Quinaprilat is eliminated primarily via the kidneys, the effective accumulation half-life is approx. 3 h, the dissociation half-life of ACE approx. 25 hours. Normal quinapril and quinaprilat plasma levels were found in patients with renal insufficiency with a creatinine clearance up to 60 ml/min. With creatinine clearance less than 60 ml/min, the quinaprilat levels increase, the time until the plasma level maximum is reached, is prolonged, the elimination half-life is also prolonged.
Pharmacokinetic studies in patients with terminal kidney diseases, who required chronic hemodialysis or were treated with outpatient peritoneal dialysis showed that dialysis only has a slight influence 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 serious heart failure. The slowing correlates with an impairment of renal function, which 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 observed in patients with liver cirrhosis, attributable to a reduced metabolization of quinapril in its passage through the liver.
- *Hydrochlorothiazide*

Hydrochlorothiazide is absorbed to 60-80 % after oral administration. Peak plasma concentrations of hydrochlorothiazide of 70 ng/ml were reached 1.5-4 hours after oral administration of 12.5 mg hydrochlorothiazide. 142 ng/ml 2-5 hours after 25 mg hydrochlorothiazide p.o. and 260 ng/ml 2-4 hours after 50 mg hydrochlorothiazide p.o.
65% of hydrochlorothiazide are bound to plasma proteins; the relative distribution volume is 0.5-1.1 l/kg.
Hydrochlorothiazide is excreted almost completely as a substance with the urine (more than 95 %), after an oral single dose; 50-70 % of the dose are excreted within 24 hours and detectable quantities appear in the urine already after 60 minu-tes.
The elimination half-life is 6-8 hours.
A decreased excretion and prolongation of the half-life are observed in kidney failure. Renal clearance of hydrochlorothiazide shows a close correlation to creatinine clearance.

There is no relevant change in the pharmacokinetics of hydrochlorothiazide in liver cirrhosis. No studies of interaction in patients with heart failure.
12.4 Bioavailability
- *Quinapril*

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

The bioavailability of hydrochlorothiazide is approx. 70 % after oral administration.
- *Combined administration of quinapril and hydrochlorothiazide*

Accuzide film-coated tablets are bioequivalent with concurrent administration of the two individual substances.
13. Miscellaneous Notes
Use during pregnancy and lactation
Experience is inadequate concerning the safety of use of ACE inhibitors during pregnancy in humans. Cases of fetal syndrome have been reported in the past few years, characterized by serious hypoplasia of the skull bones, retardation of intrauterine growth, oligohydramnia and neonatal anuria, which may result in the death of the neonate.The hypotensive effect on the fetus during the second and third trimester of pregnancy is assumed to be the cause. Such effects are not to be expected if therapy is switched in time to other antihypertensive drugs in the first trimester.

No experience is known with the use during lactation in humans.
14. Specific Storage Instructions
store in a dry cool place not exceeding 25°C
15. How Supplied
Accuzide 20
30 film-coated tablets
16. Status of Information
March 2001
Manufactured by: Pfizer Manufacturing Deutschland GmbH - Betriebsstätte Freiburg
Mooswaldallee 1 79090 Freiburg / Germany
Registered licensee
Parke-Davis Germany

THIS IS MEDICAMENT
- Medicament is a product which effects 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 medicine, its benefits and risks.
- Do not by yourself interrupt the priod of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor

KEEP MEDICAMENT OUT OF REACH OF CHILDREN

Council of Arab Health Ministers
Union of Arab Pharmacists

449 242