Accuzide<sup>®</sup> 20 1.Description of Drug Accuzide® 20 2.Composition of Drug 2.1Category of Substance or Indication bination of angiotensin-converting-enzyme-inhibitor and thiazide diuretic, antihypertensive 2.2 Medicinally Active Ingredients Accuzide 20 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 Candeilla wax, crospovidone, hydroxypropyl cellulose, lactose 1 H<sub>2</sub>O, macrogol 400, heavy basic magnesium carbonate, magnesium stearate, methylhdroxypropyl cellulose, povidone, dl yes E 171, E 172 Essential hypertension. Accuzide film-coated tablets are indicated in patients whose hypertension could not adequately be lowered with quinapril alone. 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) Stenosis of the renal arteries (bilateral or in single kidney) Status after kidney transplantation emodynamically relevant aortic or mitral valve stenosis or hypertrophic cardiomyopathy Compensated heart failure Primary hyperaldosteronism Serious impairment of hepatic function (precoma/coma hepaticum) or primary hepatic disease Sinically relevant electrolyte imbalance (hypercalcemia, hyponatremia, hypokalemia) hildren (due to a lack of therapeutic experience) Life-threatening hypersensitivity reactions may occur during LDL (low-density lipoprotein)-apheresis (in serious hypercholesterinemia) with dextrane suitate and concurrent administration O1 an ACE inhibitor. Sometimes tile-threatening hypersensitivity reactions (e.g. blood pressure fall, dyspnex, vomiting, allergic skin reactions) may occur during treatment to reduce or cancel the allergic reaction threshold (desensitization thresp) for insect toxins (such as bee or wasp sting) 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 dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made, since there is the risk during dalysis or hemofiltration that hypersensitivity reactions (anaphylactoid reactions) high-flux-membranes (e.g. "AN 69") may be made. tions) 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 bearing potential before using an ACE inhibitor combined. These women must use sequence contraception during treatment with Accuzide. It programs of determined during fractional with Accuzide, as within 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. Breastleeding 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, sclerodermia) concurrent systemic therapy with drugs which suppress the defense reactions (e.g. corticolds, cytostatics, antimetabolites), allopurinol, procainamide or lithium hypovolemia cerebral scierosis coronary sclerosie - manifest or latent diabetes mellitus mpaired henstic 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) atients with serious hypertension Patients over 65 years of age Gorresponding 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 5. Adverse Reactions The following adverse reactions were observed during therapy with Accuzide or other ACE inhibitors or hydrochlorothiazide: Decasionally, especially at the start of Accuzide therapy, and in patients with sait and/or fluid deficiency (e.g. vomiting/diarrhea, previous duretic 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 anhythmas may result requestions, terrery task to vortecutarises (synchronia) may coult. fachycardia, palpitations, chest pain, angina pectoris, myocardial infarction, TIA, cerebral hermorrhage. Cocessionally, impairments of renal function may occur or worsen, in isolated cases up to acute kidney failure, Proteinuris, 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. Occasionality dry initiative cough and branchitis, rarely dyspnea, sinustis, thinkis, in isolated cases bronchospasms, glossitis, dry mouth and hinst may occur. In isolated cases, a sudden onset of putmonary 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 angioneurotric edema in black patients. Gastrointestinal tract/Liver Occasionally nausea, upper abdominal disconfort, indigestion, rarely vomiting, diarrhea, constipation, anorexia, pancreatitis and - especially with pre-existing cholelithiasis - acute cholecystis 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, privitus or skin reactions like pemphigus, erythema multiforms, extoliative dermatritis, Stevens-Johnson syndrome, outeneous lupus erythematodes (isolated cases under hydrochiorothiazide) and toxic epidemail necrolysis or angioneurotic edema involving los, face and/or externities may count. These skin charges may be accompanied in some cases or fevere, mystains, arthraigias/arthraigia Therapy with Accuzide must be discontinued if serious skin reactions are suspected. Anaphylacticit reactions, portaistom skin changes, portaistom Thromboses and embolisms may occur farely under high does of hydrochioohiabide due to hemoconcentrations - especially in derify patients or in the presence of venous diseases. Inpaired lear secretion occurred in trare cases under hydrochiorothiazde. Occesionally due in part to imbalances in water and electrolytes - headache, fatgue, somnolence, weakness, apathy rarely depressions, piddiness, insomnila, impolence, paresthesias, dysquilibrium, 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.

Occasionally, there is a decrease in hemoglobin, hematocrit, leukocyte or thrombocyte counts.

Rarely especially in patients with impared renal function, collegen diseases or oncurrent thrapy with allopurinel, procelinamide or certain drugs which suppress the delense reactions, avenia, thrombocytopenia, leukopenia, estimophilia, in isolated cases

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

oregient hydrochlorothiazide may occasionally induce hypokalemia, hypochloremia, hypomagnesiemia, hyporalcemia, glucosuria and metabolic alkalosis. Elevations of blood sugar, cholesterol. triolycerides. uric acid, amvlase in the serum were observed Occasionally, especially in patients with impaired renal function, serum concentrations of urea, creatinine and polassium may increase and sodium concentration in the serum may decrease. Increased protein excretion in the urine may occur. In individual cases. bilinubin and hepatic enzyme concentrations may increase and repairs enzyme concentration may income the second sec Notes. The above memories ratio and blood counts should be performed at short intervals. It symptoms like fever

swollen ymph 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 the participanis in venicipal on the individual of the individual of the individual of the state 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 Accuride other ACE inhibitors or hydrochlorothiazide were described on concurrent use of:

Common salt: Decrease in antihypertensive effect of Accuzide

- common sail, becrease in aninypetensive elect of Accuzide antibypertensive (e.g. other dimension) of the antibypertensive effect of Accuzide antibypertensive (e.g. other dimension) of the antibypertensive effect of Accuzide Aminyperensives (e.g. ourse durateus, bearteophon vectors), reconstruction and a construction of the antihypertensive effect of Accuzide. Acute renal failure may be induced, especially in hypovole - analogesis, antiphologistics (e.g. salicyclic acid derivatives, indomethacin): Possible weakoning of the antihypertensive effect of Accuzide. Acute renal failure may be induced, especially in hypovole - High-dose salicylate administration: Potentiation of toxic CNS effects of salicylates due to hydrochlorothlaz

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 pota 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

Dipitalis 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

atecholamines (e.g. epinephrine): Reduction of effect due to hydrochlorothiazide

- Kaliuretic diuretics (e.g. lurosemide), glucocorticoids, ACTH, carbenoxolon, amphotericin B, penicillin G, salicylates or laxative abuse: Increased potassium and/or magnesium loss due to hydrochlorothiazide plestvramine or colestipol: Reduced absorption of hydrochlorothiazide

Allopurinol, cytostatics, immunosuppressants, systemic corticoids, procainamide: Decrease in leukocyte count in the blood, leukopenia

tostatics (e.g. cyclophosohamide, 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 hemolyses due to formation of antibodies to hydrochlorothlazide

uroleptics, imipramin: Potentiation of the antihypertensive effects of quinapril

etracyclines: Reduced absorption of tetracyclines

. realingse Accuzide should not be used with polyacryinitri-methallylsullonate-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 Incompatibilit

mpatibilities 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. guinapril and hydrochlorothiazide). If clinically appropriate, a direct change from monotherapy to the fixed combination can be considered.

substances (i.e. quantum in hydrokonomickance), i comcany i composition of the combination Accuzide - especially in patients with salt and/or fluid deliciency (e.g. vomiting/diarrhea, prior diuretic treatment), severe hypertension these patients must be monitored for at least 6 hours.

Accuzide 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 guinapril and 12.5 mg hydrochlorothiazide) in the morning. A dose of 1 film-coated tablet Accuzide per day should not be exceeded. The solar daily dose to paints in which a command have been as the solar daily dose to paints in any density in a real 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 (litration of the individual ingredients). Therapy of patients with mild renal failure (creatinine clearance 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. Control of blood pressure can then be continued with Accuzide. Patients with serious renal failure (creatinine clearance less than 30 ml/min) are to he excluded from treatment with Accuzid

### 10 Mode and Duration of Administratio

Accuzide can be taken independent of meals. The indicated 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 Antidote 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 (otlow 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 the 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. aastric lavage, administration of absorberts and sodium sultate within 30 minutes after ingestion of Accuzide), the vital parameters must be monitored or corrected under intensive medical conditions. Quinapril and hydrochivrothiazide cannot be quantitatively dialyzed. In cases of hypotension, saline and volume substitution should lifst be initiated if the response is not adequate, additional catecholamines should be administered intravenously. Therapy with angiotensin II should be considered. Pacemaker 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. 2. Pharmacological and Toxicological Properties, Pharmakocinetics and Bioavailability, as far as such data are required for the rapeutic use

12.1 Pharmacological Properties

## Accuzide has both antihypertensive and diuretic effects.

Autonomical and hydrochiorothiazide 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 hydrochiorothiazide. Mechanism of action

- Company is hydrolyzed in the liver to guinaprilat, 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 Companies injuication of ACE results in reduced formation of the vasoconstrictive angiotensin II in tissues and plasma, resulting in a decrease of adosterone secretion and thus an increase in serum polassium concentration. Elevation of plasma-renin activity results from the cancelan infolution of ACE results in decorption of the decorption of th 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

- ryuncelinormazies hereating and the state of the state luminal cell membrane. Potassium and magnesium excretion is increased, calcium excretion reduced. Hydrochlorothiazide produces low hydrogen carbonale 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

Quinanril

In hypertensive patients, guinapril leads to a reduction of blood pressure both in the supine and standing positions, without a compensatory increase in heart rate.

In hemodynamic studies, guinapril produced 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 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).

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

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 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 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 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 884 mg/kg BW after intravenous administration. istration of the suspension and 3130 mg/kg BW after intraperlioneal 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

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 hiohest

dose. Some animals developed gastric erosions; local 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.

Reproduction toxicity Studies with doses up to 300 mg/kg BW/day in rats and 1.5 mg/kg BW/day in ratbits, respectively revealed no evidence of a teratogenic potential. Whereas no embryotoxic effects were observed in rats, maternal-loxic and embryotoxic effects occurred

in rabbits starting at a dose of 1 mg/kg BW/day. On administration during fetal 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.

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 seri-

ous hypoclasia of skull bones, retardation of intrauterine growth, oligohydramnia and neonatal anuna, 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

The LD50 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).

Acute 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

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 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 carringnenic effect was observed in male and female rats or in temple mice to 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

Hydrochlorothlazide passes the placental barrier in animal experiments. Studies in 3 animal species (rats, mice, rabbits) showed no evidence of a teratogenic 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 muce with daily doses of 75 and 100 mg/kg BW, respectively.

Quinapril was not mutagenic in adequate investigation of gene and chromosome mutation tests in vitro and in vivo.

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 guinapril 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 degs 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 guinapril alone

These toxic effects of the combined administration of guinapril 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 maternal weight gain was reduced. The mean body weight of female rat fetuses was reduced at doses starting with 5/3.1 mg/kg BW/day. This weight reduction occurred in fetuses of both sexes 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 penetration of placenta.

## 12.3 Pharmacokinetic

Maximum quinapril 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 quinapril. lat. In addition, some other, quantitatively unimportant and pharmacologically inactive metabolities are produced. Maximum plasma levels of quinaprilat, the active metabolitie, are observed approx, 2-3 h after oral administration of quinapril. Protein binding of quinapril and guinaprilat is approx. 97 %. Approx. 60 % of a guinapril 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. 26 hours. Normal guinapril and aunaprilat plasma levels were found in patients with renal insufficiency with a creatinine clearance up to 60 mil/min. With creatinine clearance less than 60 mil/min, the guinaprilat 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 mi/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

### - 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 no/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.

Hydrochiorothiazide is excreted almost completely unchanged via the kidneys (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 creatining clearance

There is no relevant change in the pharmacokinetics of hydrochlorothiazide in liver cirrhosis. No studies of hydrochlorothiazide kinetics were performed in patients with heart failure.

# 12.4 Bioavailability

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

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, eligohydramnia 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 trimeste

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 Manufactured by: Pfizer Manufacturing Deutschland GmbH - Betriebsstätte Freiburg Mooswaldallee 1 79090 Freiburg / Germany **®registered trademark** Parke-Davis Germany

THIS IS 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 medicine, its benefits and risks. Do not by yourself interrupt the pried 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