The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if needed, the dose should then be increased to losartan 100 mg/hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg/hydrochlorothiazide 25 mg once daily. HYZAAR and FORTZAAR are suitable alternative formulations in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide in the same dosages.

4.3 Contraindications
HYZAAR is contraindicated in:
- patients who are hypersensitive to any component of this product
- patients who are hypersensitive to other sulfonamide-derived drugs
- patients with anuria.

4.4 Special warnings and special precautions for use
Losartan
Hypersensitivity: Angioedema. See Side Effects
Symptomatic Hypotension
HYZAAR should not be initiated in patients who are intravascularly volume-depleted because symptomatic hypotension may occur. Such situations are most likely in patients who are being treated with high-dose diuretics, are on a low-sodium diet or are experiencing vomiting or diarrhea. In patients with concurrent heart insufficiency there may be an increased risk of symptomatic hypotension. This is true in particular for severe forms of heart insufficiency as may be manifest from the concomitant use of high-dose diuretics, hyponatremia or renal impairment. In such patients, treatment should preferably be initiated in the hospital. In general, intravascular volume depletion should be corrected prior to administration of losartan.

No initial dosage adjustment is necessary for elderly patients.
Renal Function Impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported in susceptible individuals; these changes in renal function may be reversible upon discontinuation of the therapy.

Other drugs that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with losartan.

Hemodialysis patients
Pharmacokinetic data indicate that the plasma concentration of losartan is highly variable in this patient group, and on average is significantly higher than in other patients.

Hepatic Disease
Based on pharmacokinetic data significantly increased plasma concentrations of losartan in cirrhotic patients are demonstrated.

Operation/narcosis
In patients undergoing major surgery, or during narcosis with agents causing hypotension, losartan blocks the action of angiotensin II after compensatory renin secretion. If hypotension occurs, which may be attributed to this mechanism, it may be corrected by volume replenishment.

Hydrochlorothiazide
Hypotension and Electrolyte/Fluid Imbalance
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients but is more likely in the presence of fluid or electrolyte imbalance. Periodic determination of serum electrolytes should be performed at appropriate intervals as in any patient receiving diuretics.

Renal Function Impairment
Thiazides are not appropriate diuretics for use in patients with renal impairment, and are ineffective at creatinine clearance values of 30 ml/min or below (i.e., moderate or severe renal insufficiency).

Hepatic Disease
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Metabolic and Endocrine Effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see ‘Interaction with other medicaments and other forms of interaction’). Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan produces a slight decrease in uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia to some degree.

Other precautions.
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Hyzaar
Pediatric Use
HYZAAR has not been studied in children.

Lactose
HYZAAR contains lactose and therefore should not be used by patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. HYZAAR contains less than 70 mg of lactose per tablet.
4.5 Interaction with other medicinal products and other forms of interaction

**Losartan**

**Other hypertensives**

Concurrent use with other antihypertensives may potentiate the antihypertensive effect.

**Lithium**

Although no specific research has been performed, losartan may reduce lithium excretion. That is why serum lithium levels should be carefully monitored when administering lithium salts.

**Other drugs**

Losartan is converted into the active carboxyl acid metabolite primarily by cytochrome P450 (CYP) 2C9. Repeated administration of fluconazole, a CYP2C9 inhibitor caused approximately 50% reduction in active metabolite AUC in an interaction study with healthy volunteers. The clinical consequence of this is as yet unknown. Concomitant administration of fluvastatin, a mild CYP2C9 inhibitor, caused no clinically relevant interaction.

Other interaction studies show that the cytochrome P450-3A4 inhibitors ketoconazole, itraconazole and erythromycin do not affect the metabolism of losartan. Phenobarbital, a metabolism enzyme inducer, has no clinically relevant influence on losartan metabolism. However, concomitant administration of inducer rifampin achieved a 40% reduction in the plasma concentration of the active metabolite. The clinical relevance of this is as yet unknown.

No clinically relevant drug interactions have been found with hydrochlorothiazide, digoxine, warfarine and cimetidine in clinical pharmacokinetic trials.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

The antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs (NSAID’s).

**Hydrochlorothiazide**

When given concurrently with the following drugs, interactions may occur:

**Alcohol, Barbiturates, or Narcotics**

Potentiation of orthostatic hypotension may occur.

**Antidiabetic Drugs (Oral Agents and Insulin)**

Dosage adjustment of the antidiabetic drug may be required.

**Other Antihypertensive Drugs**

Additive effect.

**Cholestyramine and Colestipol Resins**

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

**Corticosteroids, ACTH**

Intensified electrolyte depletion, particularly hypokalemia may occur.

**Pressor Amines (e.g., Epinephrine)**

Possible decreased response to pressor amines but not sufficient to preclude their use.

**Skeletal Muscle Relaxants, Nondepolarizing**

Possible increased responsiveness to tubocurarine.

**Lithium**

Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended. Refer to the package inserts for lithium preparations before use of such preparations.

**Prostaglandin Synthetase Inhibitors**

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

**Drug/Laboratory Test Interactions**

Although no specific research has been performed, it is to be expected that serum potassium could increase with concomitant use of potassium supple-
ments and salt substitutes containing potassium, particularly in patients with renal impairment. Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see ‘Special warnings and special precautions for use’).

4.6 Pregnancy and lactation

Use during Pregnancy

There are insufficient data on the use of HYZAAR during pregnancy in man to evaluate potential harmfulness. In animal experiments losartan proved to be harmful. When losartan was administered to rats during late gestation or during lactation, it produced renal abnormalities, reduced body weight and increased mortality in offspring.

On the basis of the pharmacologic action of losartan, harmfulness due to use in pregnancy is possible. The mechanism of this is believed to be pharmacologically mediated through the effects of the renin-angiotensin system. Fetal and neonatal morbidity and mortality can be caused by ACE inhibitors when administered to pregnant women during the second and third trimesters of pregnancy. Use of drugs that directly act on the renin-angiotensin system during this period have been associated with fetal and neonatal disorders, including hypotension, renal insufficiency, hyperkalemia and/or skull hypoplasia. As a result of reduced renal function, oligohydramnios may occur in the fetus. This may lead to limb contractures, craniofacial deformations and hypoplastic lung development. While no data are available, this could also occur with angiotensin II receptor antagonists.

The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

From clinical observations it has appeared that thiazides may be harmful to the fetus. Thiazides cross the placental barrier and appear in the cord blood. The possible hazards to the fetus include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

If children are desired and in case of pregnancy, HYZAAR should be discontinued as soon as possible. Furthermore, patient should immediately contact the treating physician in order to decide on an alternative treatment. It would be wise to point this out to the patient at the start of treatment.

Use during Lactation

Thiazides appear in human milk. It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

There are no known data on the effect on the ability to drive. In view of the possible occurrence of the side effect dizziness, one should take negative effect on the ability to drive and operate machines into account.

4.8 Undesirable effects

The side effects reported in the combined use of losartan potassium and hydrochlorothiazide are generally mild and transient and do not give rise to discontinuation of treatment. The occurrence of dizziness, headache and asthenia/fatigue are the main side-effects in the use of HYZAAR. Also the side-effects of the separate ingredients should be taken into account; these include palpitation, nausea, rash, sweating, myalgia, abdominal pain, migraine, anemia, and liver function abnormalities.

The following adverse reactions have been reported in post-marketing experience:

Hypersensitivity: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue has been report-
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combination products (antihypertensive agents), ATC Code: C09DA 01

Losartan - Potassium

The components of HYZAAR have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. As a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, aldosterone secretion, and the levels of angiotensin II and decreases serum potassium, while losartan blocks all physiologically relevant effects of angiotensin II, including inhibition of aldosterone secretion; this could attenuate the potassium loss associated with the use of hydrochlorothiazide.

Generally losartan causes a slight decrease in serum uric acid which is persistent in chronic therapy. Hydrochlorothiazide has been shown to cause modest increases in uric acid. When the combination was used, an elevation of uric acid was observed, although somewhat less frequently than with hydrochlorothiazide alone.

The antihypertensive effect of HYZAAR is sustained for a 24-hour period. In clinical studies of at least one year’s duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of HYZAAR had no clinically significant effect on heart rate.

A study in patients with severe hypertension showed the utility of HYZAAR administered as initial therapy and in a regimen with other antihypertensive agents after 12 weeks of therapy.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

4.9 Overdose

No specific information is available on the treatment of overdosage with HYZAAR. Treatment is symptomatic and supportive. Therapy with HYZAAR should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Losartan

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.
Losartan
Losartan belongs to a new class of antihypertensives and is an effective, synthetic, orally active angiotensin II receptor antagonist. Angiotensin II, a potent vasoconstrictor, is the active hormone of the renin-angiotensin system and a major determinant in the pathophysiology of hypertension. Angiotensin II also stimulates smooth muscle cell proliferation. Angiotensin II binds to the AT1 receptor found in many tissues (e.g., vascular smooth muscles, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. AT2 receptors are not blocked by losartan.

Both losartan and the pharmacologically active metabolite bind selectively to the AT1 receptor. Losartan and its active metabolite have no agonist effects. Losartan does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Losartan differs from ACE inhibitors in that it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with the ACE inhibitor lisinopril. In comparative research, there was no evidence of the occurrence of cough in patients given losartan.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

LIFE Study
The Losartan Intervention for Endpoint Reduction (LIFE) study was a randomized, double-blind study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomized to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure was (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach goal blood pressure. In efforts to control blood pressure, the patients in both arms of the LIFE study were coadministered hydrochlorothiazide the majority of time they were on study drug (73.9% and 72.4% of days in the losartan and atenolol arms, respectively).

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke, and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Systolic blood pressure showed a significant 1.7 mmHg difference in favor of losartan and diastolic blood pressure showed a nonsignificant 0.2 mmHg difference in favor of atenolol.

Treatment with losartan resulted in a risk reduction from 13% to 11% (relative risk reduction 13%, p=0.021, 95% confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. Treatment with losartan reduced the risk of stroke from 7% to 5% (relative risk reduction 25%, p=0.001). The rates of cardiovascular death and myocardial infarction were not significantly different between treatment groups. Patients treated with losartan had significantly greater reduction in ECG indices of left ventricular hypertrophy as compared to patients treated with atenolol. Losartan was well tolerated. The most common drug related adverse events were dizziness, asthenia/fatigue and vertigo. Adverse effects, particularly bradycardia, cool extremities, and sexual dysfunction, were noted significantly less often in losartan treated patients than in patients treated with atenolol. Losartan was well tolerated. The most common drug related adverse events were dizziness, asthenia/fatigue and vertigo. Adverse effects, particularly bradycardia, cool extremities, and sexual dysfunction, were noted significantly less often in losartan treated patients than in patients treated with atenolol. Dizziness was the most frequently reported adverse event (losartan 16% and atenolol 15%). Discontinuation due to drug-related adverse events was significantly less common in the losartan group than in the atenolol group. In the LIFE study, among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with
Distribution

Losartan
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier. Hydrochlorothiazide is excreted in human milk.

Biotransformation

Losartan
About 14% of an intravenously -or orally- administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labeled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. The conversion of losartan into the active metabolite is primarily catalyzed by the enzyme cytochrome P450 2C9. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N 2 tetrazole glucuronide.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized.

Elimination

Losartan
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively.

When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.
The terminal half-life of losartan and the active metabolite is about 2 hours and 6-9 hours, respectively. During once-daily dosing, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of $^{14}$C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

**Hydrochlorothiazide**

Hydrochlorothiazide is eliminated rapidly by the kidney. The plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

**Characteristics in Patients**

**Losartan**

The plasma concentrations of losartan and its active metabolite in elderly hypertensives are not statistically significantly different from those in young hypertensives. The plasma concentrations of losartan in hypertensive patients are statistically significantly higher in women in comparison with men. Concentrations of the active metabolite are similar in men and women.

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Neither losartan nor the active metabolite can be removed by hemodialysis.

**Hydrochlorothiazide**

The plasma concentrations of hydrochlorothiazide in hypertensive patients with reduced renal function are statistically significant higher in comparison to patients with normal renal function.

**5.3 Preclinical safety data**

In animal experiments, losartan had a negative effect on late-fetal development (see ‘Use during pregnancy and lactation’). Otherwise there are no specific data.