

NEW ZEALAND DATA SHEET

Name of Medicine

HYZAAR[®]

losartan potassium (MSD) and hydrochlorothiazide (BP/USP)
50/12.5 mg tablet

Presentation

A yellow oval shaped film-coated tablet with 717 on one side and plain on the other.
Dimensions 11.21 mm x 6.05 mm.

Therapeutic Class

HYZAAR (losartan potassium/HCTZ) is the first combination of an angiotensin II receptor antagonist (type AT₁) and a diuretic.

Indications

Hypertension

HYZAAR is indicated for the treatment of hypertension, for patients in whom combination therapy is appropriate.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

HYZAAR is a combination of losartan (COZAAR) and hydrochlorothiazide. In patients with hypertension and left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, reduces the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy (see Warnings and Precautions, *Race*).

Dosage and Administration

HYZAAR may be administered with other antihypertensive agents.

HYZAAR may be administered with or without food.

Hypertension

The usual starting and maintenance dose of HYZAAR (losartan 50 mg/HCTZ 12.5 mg) is one tablet once daily. For patients who do not respond adequately to HYZAAR, the dosage may be increased to two tablets once daily. The maximum dose is two tablets once daily. In general the antihypertensive effect is attained within three weeks after initiation of therapy.

HYZAAR should not be initiated in patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics).

HYZAAR is not recommended for patients with severe renal impairment (creatinine

clearance ≤ 30 mL/min) or for patients with hepatic impairment.

No initial dosage adjustment of HYZAAR is necessary for elderly patients.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

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 and hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg and hydrochlorothiazide 25 mg once daily. HYZAAR 50/12.5 is a suitable alternative formulation in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

*Note: Hydrochlorothiazide is not available in New Zealand

Contraindications

HYZAAR is contraindicated in:

- patients who are hypersensitive to any component of this product
- patients with anuria
- patients who are hypersensitive to other sulphonamide derived medicines

Warnings and Precautions

Losartan-Hydrochlorothiazide

Hypersensitivity: Angioedema. See Adverse Effects

Hepatic and Renal Impairment

HYZAAR is not recommended for patients with hepatic impairment or severe renal impairment (creatinine clearance ≤ 30 mL/min) (see Dosage and Administration).

Losartan

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 therapy.

Other medicines 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; these changes may be reversible upon discontinuation of therapy.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see Interactions).

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia 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 hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.

Other

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.

Pregnancy

When used in pregnancy during the second and third trimesters, medicines that act directly on the renin-angiotensin system can cause injury and even death in the developing foetus. When pregnancy is detected, HYZAAR should be discontinued as soon as possible.

Although there is no experience with the use of HYZAAR in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system. In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin system, begins in the second trimester; thus, risk to the foetus increases if HYZAAR is administered during the second or third trimesters of pregnancy.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Nursing Mothers

It is not known whether losartan is excreted in human milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the medicine, taking into account the importance of the medicine to the mother.

Paediatric Use

Safety and effectiveness in children have not been established.

Use in the Elderly

In clinical studies there were no clinically significant differences in the efficacy or safety profiles of HYZAAR in older (≥ 65 years) and younger (< 65 years) patients.

Race

Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of losartan on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in Black patients. In the overall LIFE study population ($n=9193$), treatment with losartan resulted in a 13.0% risk reduction ($p=0.021$) as compared to atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. In this study, losartan decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy ($n=8660$) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction ($p=0.003$). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with losartan ($p=0.03$). In the subgroup of Black patients ($n=533$; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 25.9 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 41.8 per 1000 patient-years) on losartan.

Animal Toxicology

Carcinogenesis

Losartan

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

Hydrochlorothiazide

Two-year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice.

Mutagenesis

Losartan-Hydrochlorothiazide

Losartan potassium-hydrochlorothiazide was negative in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution assay in rat hepatocytes and *in vitro* chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations.

Losartan

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays at concentrations that

were approximately 1700 times greater than the maximum plasma level achieved in man at the recommended therapeutic dosage level. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (4500 mg/m²) (750 times the maximum recommended daily human dose). In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Hydrochlorothiazide

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Reproduction

Losartan-Hydrochlorothiazide

Losartan potassium-hydrochlorothiazide administration had no effect on the reproductive performance or fertility in male rats at dosage levels of up to 135 mg/kg/day of losartan in combination with 33.75 mg/kg/day of hydrochlorothiazide. These dosage levels provided respective plasma concentrations (AUC) for losartan, the active metabolite and hydrochlorothiazide that were approximately 260-, 120-, and 50- fold greater than those achieved in man with 50 mg of losartan potassium in combination with 12.5 mg hydrochlorothiazide. In female rats, however, the coadministration of losartan potassium/hydrochlorothiazide (10/2.5 mg/kg/day) induced a slight but statistically significant decrease in fecundity and fertility indices. Compared to plasma concentrations in man (see above) these dosage levels provided respective increases in plasma concentration (AUC) for losartan, the active metabolite, and hydrochlorothiazide of approximately 15-, 4-, and 5-fold.

Losartan

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.

Hydrochlorothiazide

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Development

Losartan-Hydrochlorothiazide

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium-hydrochlorothiazide. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F₁ generation, was observed when females were treated prior to

and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including decreased body weight and renal toxicity, also occurred when pregnant rats were treated with losartan potassium-hydrochlorothiazide during late gestation and/or lactation.

Losartan

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates. The effects include decreased body weight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to medicine exposure in late gestation and during lactation.

Hydrochlorothiazide

Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the maximum human dose) showed no evidence of external abnormalities of the foetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4-5.6 mg/kg/day (approximately 2-3 times the maximum recommended human dose) did not impair fertility or produce birth abnormalities in the offspring.

Effects on Ability to Use and Drive Machines

There are no data to suggest that HYZAAR affects the ability to drive and use machines.

Adverse Effects

In clinical trials with losartan potassium - hydrochlorothiazide, no adverse experiences peculiar to this combination medicine have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo.

In general, treatment with losartan potassium - hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as medicine related that occurred with an incidence greater than placebo in one percent or more of patients treated with losartan potassium - hydrochlorothiazide.

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, was generally well tolerated. The most common medicine-related side effects were dizziness, asthenia/fatigue, and vertigo.

The following additional adverse reactions have been reported in post-marketing experience with HYZAAR and/or in clinical trials or post-marketing use with the individual components:

Blood and the lymphatic system disorders: Thrombocytopenia anaemia, aplastic anaemia, haemolytic anaemia, leukopenia, agranulocytosis.

Immune system disorders: 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 reported rarely in patients treated with losartan; some of these

patients previously experienced angioedema with other medicines including ACE inhibitors.

Metabolism and nutrition disorders: Anorexia, hyperglycaemia, hyperuricaemia, electrolyte imbalance including hyponatraemia and hypokalaemia.

Psychiatric disorders: Insomnia, restlessness

Nervous system disorders: Dysgeusia, headache, migraine, paraesthesias

Eye disorders: Xanthopsia, transient blurred vision.

Cardiac disorders: Palpitation, tachycardia.

Vascular disorders: Dose-related orthostatic effects, necrotising angiitis (vasculitis) (cutaneous vasculitis).

Respiratory, thoracic and mediastinal disorders: Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, respiratory distress (including pneumonitis and pulmonary oedema).

Gastrointestinal disorders: Dyspepsia, abdominal pain, gastric irritation, cramping, diarrhoea, constipation, nausea, vomiting, pancreatitis, sialoadenitis.

Hepato-biliary disorders: Hepatitis, jaundice (intrahepatic cholestatic jaundice).

Skin and subcutaneous tissue disorders: Rash, pruritus, purpura (including Henoch-Schoenlein purpura), toxic epidermal necrolysis, urticaria, erythroderma, photosensitivity, cutaneous lupus erythematosus

Musculoskeletal and connective tissue disorders: Back pain, muscle cramps, muscle spasm, myalgia, arthralgia.

Renal and urinary disorders: Glycosuria, renal dysfunction, interstitial nephritis, renal failure.

Reproductive system and breast disorders: Erectile dysfunction/impotence.

General disorders and administration site conditions: Chest pain, oedema/swelling, malaise, fever, weakness.

Investigations: Liver function abnormalities.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of HYZAAR. Hyperkalaemia (serum potassium >5.5 mEq/L) occurred in 0.7% of patients, but in these trials, discontinuation of HYZAAR due to hyperkalaemia was not necessary. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

Interactions

Losartan

In clinical pharmacokinetic trials, no medicine interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (see Hydrochlorothiazide - *Alcohol, barbiturates, or narcotics* below), ketoconazole and erythromycin. Rifampin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other medicines 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.

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive medicines. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the renin-angiotensin-aldosterone system is associated with a higher frequency of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g., by adding an ACE inhibitor to an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function.

Hydrochlorothiazide

When given concurrently the following medicines may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: potentiation of orthostatic hypotension may occur.

Antidiabetic medicines (oral agents and insulin): dosage adjustment of the antidiabetic medicine may be required.

Other antihypertensive medicines: 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 or glycyrrhizin (found in liquorice): intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. adrenaline): possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarising (e.g. tubocurarine): possible increased responsiveness to the muscle relaxant.

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 insert for lithium preparations before use of such preparations.

Non-steroidal anti-inflammatory medicines: Including Cyclooxygenase-2 Inhibitors: The administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Medicine/Laboratory Test Interactions

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see Warnings and Precautions).

Overdosage

Losartan potassium

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 if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma 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. If symptomatic hypotension should occur, supportive treatment should be instituted.

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.

Actions

Pharmacodynamic Properties

Losartan - Hydrochlorothiazide

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. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricaemia.

Losartan and hydrochlorothiazide, when used in combination are additive in their antihypertensive efficacy.

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. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

In a study comparing the combination of losartan 50 mg/hydrochlorothiazide 12.5 mg with the combination captopril 50 mg/hydrochlorothiazide 25 mg in young (<65 years) and elderly (≥65 years) hypertensive patients, the antihypertensive responses were similar between the two treatments and by age groups. Overall, there were statistically significantly fewer medicine-related clinical adverse experiences and discontinuations due to clinical adverse events with losartan 50 mg/hydrochlorothiazide 12.5 mg than with captopril 50mg/hydrochlorothiazide 25 mg.

A study with 131 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.

HYZAAR is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

Pharmacokinetic Properties

Absorption

Losartan

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the medicine was administered with a standardised meal.

Distribution

Losartan

Both losartan and its active metabolite are $\geq 99\%$ bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. 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 and is excreted in breast 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 ^{14}C -labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. 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.

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.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, 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 -labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, 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-Hydrochlorothiazide

The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan

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 haemodialysis.

Pharmaceutical Precautions

Store at temperatures below 30°C.

Medicine classification

Prescription Medicine

Package Quantities

HYZAAR (50 mg/12.5 mg) tablets are available in blister packs of 30 tablets each.

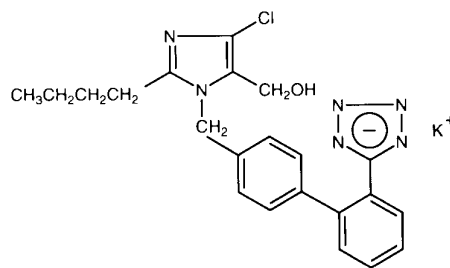
Further Information

Chemistry

Losartan Potassium

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-methanol monopotassium salt.

Its empirical formula is $\text{C}_{22}\text{H}_{22}\text{ClKN}_6\text{O}$, and its structural formula is:

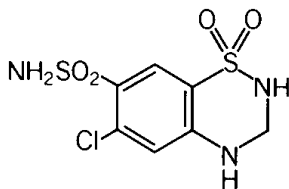


Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Hydrochlorothiazide

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Inactive Ingredients

Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinised starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, quinoline yellow aluminium lake, titanium dioxide, carnauba wax.

HYZAAR 50/12.5 contains 4.24 mg (0.108 mEq) of potassium.

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Date of Preparation

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