Important information. Please read carefully.

XYCOVAA Film-Coated Tablet
50mg & 100mg

COMPOSITION

Xycovaa Film-Coated Tablet 50mg: Each tablet contains Losartan Potassium 50mg.

Xycovaa Film-Coated Tablet 100mg: Each tablet contains Losartan Potassium 100mg.

PHARMACODYNAMICS

Pharmacodynamic properties

Losartan inhibits systolic and diastolic pressor responses to angiotensin II infusions. At peak, 100 mg of losartan potassium inhibits these responses by approximately 85%; 24 hours after single and multiple-dose administration, inhibition is about 26-39%.

During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. During chronic (6 weeks) treatment of hypertensive patients with 100 mg/day losartan, approximately 2-3 fold increases of plasma angiotensin II were observed at time of peak plasma drug concentrations. In some patients, greater increases were observed, particularly during short term (2 weeks) treatment. However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent at 2 and 6 weeks, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined to untreated levels within 3 days.

Since losartan is a specific antagonist of the angiotensin II receptor type AT1, it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. In a study which compared the effects of 20 mg and 100 mg of losartan potassium and an ACE inhibitor on responses to angiotensin I, angiotensin II and bradykinin, losartan was shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin. This finding is consistent with losartan's specific mechanism of action. In contrast, the ACE inhibitor was shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

Plasma concentrations of losartan and its active metabolite and the antihypertensive effect of losartan increase with increasing dose. Since losartan and its active metabolite are both angiotensin II receptor antagonists, they both contribute to the antihypertensive effect.

In a single-dose study in normal males, the administration of 100 mg of losartan potassium, under dietary high- and low-salt conditions, did not alter glomerular filtration rate, effective renal plasma flow or filtration fraction. Losartan had a natriuretic effect which was more pronounced on a low-salt diet and did not appear to be related to inhibition of early proximal reabsorption of sodium. Losartan also caused a transient increase in urinary uric acid excretion.

In nondiabetic hypertensive patients with proteinuria (≥ 2 g/24 hours) treated for 8 weeks, the administration of losartan potassium 50 mg titrated to 100 mg significantly reduced proteinuria by 42%. Fractional excretion of albumin and IgG also was significantly reduced. In these patients, losartan maintained glomerular filtration rate and reduced filtration fraction.

In postmenopausal hypertensive women treated for 4 weeks, 50 mg of losartan potassium had no effect on renal or systemic prostaglandin levels.

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

Losartan potassium, administered in doses of up to 150 mg once daily, did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL-cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

Generally losartan caused a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy. In controlled clinical trials in hypertensive patients, no patients were discontinued due to increases in serum creatinine or serum potassium.

In a 12-week, parallel-design study in patients with left ventricular failure (New York Heart Association Functional Classes II-IV), most of whom were receiving diuretics and/or digitalis, losartan potassium administered in once-daily doses of 2.5, 10, 25 and 50 mg was compared to placebo. The 25 mg and 50 mg doses produced positive hemodynamic and neurohormonal effects which were maintained for the length of the study. Hemodynamic responses were characterized by an increase in cardiac index and decreases in: pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate. The occurrence of hypotension was dose related in these heart failure patients. Neurohormonal results were characterized by a reduction in circulating levels of aldosterone and norepinephrine

PHARMACOKINETICS

Pharmacokinetic properties

Absorption

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 drug was administered with a standardized meal.

Distribution

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.

Metabolism

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. 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

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 14C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous dose of 14C-labeled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the feces.

Characteristics in Patients

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

Plasma concentrations of losartan were up to 2-fold higher in female hypertensives as compared to male hypertensives. Concentrations of the active metabolite were not different in males and females. This apparent pharmacokinetic difference is not judged to be of clinical significance.

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.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 mL/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in hemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor the active metabolite can be removed by hemodialysis.

INDICATIONS

- Hypertension

  Xycovaa is indicated for the treatment of hypertension.

- Hypertensive patients with left ventricular hypertrophy

  Xycovaa is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients.

- Nephropathy in Type 2 Diabetic Patients

  Indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio 300mg/g or more) in patients with type 2 diabetes and a history of hypertension. In this population, Xycovaa reduces the rate of progression of nephropathy as measured by the occurrence of doubling the serum creatinine or end stage renal disease (need for dialysis or renal transplantation) or death.

DOSAGE AND ADMINISTRATION

Xycovaa may be administered with or without food.

Xycovaa may be administered with other antihypertensive agents.

- Hypertension

  The usual starting and maintenance dose is 50mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100mg once daily.

  For patients with intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25mg once daily should be considered. (See Warnings and Precautions).

  No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment (See Warnings and Precautions).

- Hypertensive patients with left ventricular hypertrophy

  The usual starting dose is 50mg of Xycovaa once daily. A low dose of hydrochlorothiazide should be added and/or the dose of Xycovaa should be increased to 100mg once daily based on blood pressure response.

- Renal Protection in Type 2 Diabetic Patients with Proteinuria and Hypertension

  The usual starting dose is 50mg once daily. The dose may be increased to 100mg once daily based on blood pressure response. Xycovaa may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

- Paediatric Use

  Neonates with a history of *in utero* exposure to Xycovaa

  If oliguria or hypotension occur, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

  Antihypertensive effects of Losartan Potassium have been established in hypertensive pediatric patients aged > 1 month to 16 years. Use of Losartan Potassium in these age groups is supported by evidence from adequate and well-controlled studies of Losartan Potassium in pediatric and adult patients as well as by literature in pediatric patients.

  The pharmacokinetics of losartan have been investigated in 50 hypertensive pediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite are generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

  In a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age, patients who weighed ≥ 20 kg to <50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed ≥ 50 kg received either 5, 50 or 100 mg of losartan daily. Losartan administration once daily lowered trough blood pressure in a dose-dependent manner. The dose response to losartan was observed across all subgroups (e.g., age, Tanner stage, gender, race). However, the lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. In this study, Losartan Potassium was generally well tolerated.

  For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients ≥ 20 to <50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients >50 kg, the starting dose is 50 mg once daily. The dose can be increased to a maximum of 100 mg once daily.

  In pediatric patients who are intravascularly volume depleted, these conditions should be corrected prior to administration of Xycovaa.

  The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

  Xycovaa is not recommended in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m2, in pediatric patients with hepatic impairment, or in neonates as no data are available.

CONTRAINDICATIONS

Xycovaa is contraindicated in patients who are hypersensitive to any component of this product. Xycovaa should not be administered with aliskiren in patients with diabetes (see Drug Interactions).

WARNINGS AND PRECAUTIONS

Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Xycovaa as soon as possible. See Pregnancy and Lactation.

Hypersensitivity:

Angioedema (see Side Effects).

Hypotension and Electrolyte/Fluid Imbalance

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of Xycovaa, or a lower starting dose should be used (see Dosage and Administration).

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalemia was higher in the group treated with Losartan as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia (see Side Effects).

Concomitant use of other drugs that may increase serum potassium may lead to hyperkalemia (see Drug Interactions).

Liver Function Impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see Dosage and Administration and Pharmacology, Pharmacokinetics).

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 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; these changes in renal function may be reversible upon discontinuation of therapy.

DRUG INTERACTIONS

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, 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 drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g.: spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium, or other drug that may increase serum potassium (e.g.; trimethoprim-containing products) may lead to increase in serum potassium.

As with other drugs 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 drugs. 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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Close monitor blood pressure, renal function, and electrolytes in patients on Losartan and other agents that affect the RAAS. Do not co-administer aliskiren with Losartan in patients with diabetes. Avoid use of aliskiren with Losartan in patients with renal impairment (GFR <60 mL/min).

Grapefruit juice contains components that inhibit CYP 450 enzymes and may lower the concentration of the active metabolite of Losartan which may reduce the therapeutic effect. Consumption of grapefruit juice should be avoided while taking Losartan.

PREGNANCY AND LACTATION

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. When pregnancy is detected, discontinue Xycovaa as soon as possible.

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

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Xycovaa as soon as possible.

These adverse outcomes are usually associated with the use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other

antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Xycovaa, unless it is considered life-saving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to Xycovaa for hypotension, oliguria, and hyperkalemia.

Lactation

It is not known whether losartan is excreted in human milk. Because many drugs are excreted in human milk and 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.

SIDE EFFECTS

Xycovaa was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

Xycovaa was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia (see Precaution, Hypotension and Electrolyte/Fluid Imbalance).

The following additional 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 reported rarely in

patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely.

Gastrointestinal: Hepatitis (reported rarely), liver function abnormalities, vomiting.

General disorders and administration site conditions: Malaise.

Hematologic: Anemia, thrombocytopenia (reported rarely).

Musculoskeletal: Myalgia, arthralgia

Nervous System/Psychiatric: Migraine, dysgeusia

Reproductive system and breast disorders: Erectile dysfunction/impotence

Respiratory: Cough.

Skin: Urticaria, pruritus, erythroderma, photosensitivity

SYMPTOMS AND TREATMENT FOR OVERDOSAGE

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 haemodialysis.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

STORAGE CONDITION

Store below 30°C. Protect from light and moisture.

SHELF LIFE

The expiry date is indicated on the packaging.

PRODUCT DESCRIPTION

Xycovaa Film-Coated Tablet 50mg:

White, oval, normal convex film -coated tablet with “Z” marking on one side and plain on reverse.

Xycovaa Film-Coated Tablet 100mg:

White, round, normal convex film -coated tablet with “Z” marking on one side and plain on reverse.

Packaging and Pack Size Available

Available in pack size of 3 x 10 tablets. Clear PVC/PVdC-Aluminium blister of 10 tablets per blister.

List of excipients

Tablet core:

Microcrystalline Cellulose, Lactose Monohydrate, Starch, Colloidal Silicon Dioxide, Magnesium Stearate

Film coat:

Hydroxypropyl Cellulose, Hypromellose, Purified Stearic Acid, Titanium Dioxide

For further information, please consult your pharmacist or physician.
Revision Date: 18-11-2024

Manufacturer and Product Registration Holder:
Xepa-Soul Pattinson (Malaysia) Sdn Bhd
1-5 Cheng Industrial Estate, 75250 Melaka, Malaysia.

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