LOCAL PRODUCT CIRCULAR LPC-OG0954F-T-102024

Tablets
COZAAR® XQ® 5/50mg Tablet & Cozaar® XQ® 5/100mg Tablet
(amlodipine camsylate/losartan potassium)

I. THERAPEUTIC CLASS

COZAAR XQ (amlodipine camsylate/losartan potassium*) is a combination of an angiotensin IIreceptor (type AT_1) antagonist and a calcium channel blocker.

* (See CLINICAL PHARMACOLOGY.)

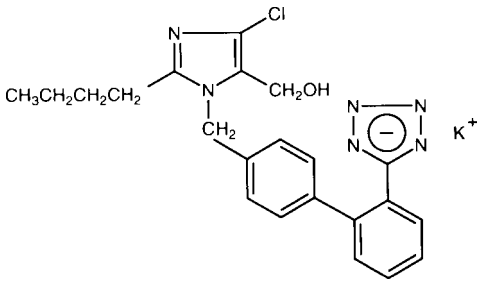
II. CHEMISTRY

COZAAR XQ contains losartan potassium and amlodipine camsylate.

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 $C_{22}H_{22}ClKN_6O$, and its structural formula is:



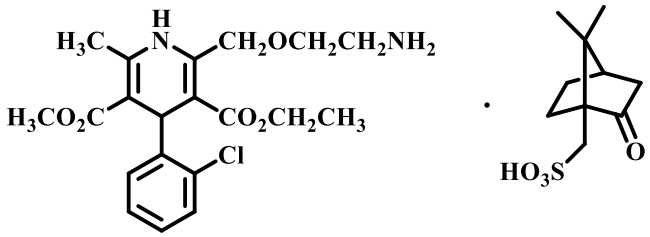
Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

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

Amlodipine camsylate

Amlodipine camsylate is chemically described as 3-ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate camphor sulfonate.

Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_{10}H_{16}O_4S$ and its structural formula is:



Amlodipine camsylate is a white to slightly yellow crystalline powder with a molecular weight of 641.17. It is freely soluble in chloroform, dimethylformamide and dimethylsulfoxide and slightly soluble in water, ethanol and methylenechloride.

III. COMPOSITION

IIIa. Active Ingredients

5/50 mg tablets: COZAAR XQ is supplied as a white, modified capsule shaped, film-coated tablet containing 50 mg of losartan potassium (equivalent to 45.8 mg losartan) and 7.84 mg amlodipine camsylate (equivalent to 5 mg amlodipine).

5/100 mg tablets: COZAAR XQ is supplied as a pink, modified capsule shaped, film-coated tablet containing 100 mg losartan potassium (equivalent to 91.5 mg losartan) and 7.84 mg amlodipine camsylate (equivalent to 5 mg amlodipine).

IIIb. Inactive Ingredients

Each tablet contains the following inactive ingredients: butylated hydroxytoluene, sodium starch glycolate, microcrystalline cellulose, D-mannitol, povidone, crospovidone, magnesium stearate, hypromellose, hydroxypropylcellulose, titanium oxide, and talc.

COZAAR XQ 5/100 mg tablets also contain iron oxide red and iron oxide yellow.

IV. CLINICAL PHARMACOLOGY

COZAAR XQ

The results of two bioequivalence studies in healthy subjects demonstrated that the COZAAR XQ (amlodipine/losartan) 5/50mg and 5/100mg combination tablets are bioequivalent to co-administration of corresponding doses of amlodipine camsylate and losartan potassium (COZAAR) as individual tablets with the exception of C_{max} for losartan in the 5/50mg study. This difference was not considered clinically significant.

Amlodipine

The bioequivalence of amlodipine besylate and amlodipine camsylate was evaluated in a randomized, single blind, crossover comparative study conducted in 18 healthy subjects. Groups of 9 subjects received a single 5 mg dose of amlodipine besylate or amlodipinecamsylate. Treatments were then crossed over after a 4 week washout period. All 18 subjects received both treatments and completed the study.

Pharmacokinetic parameters including t_{max}, C_{max}, AUC, and half-life were similar following single 5 mg doses of amlodipine besylate and amlodipine camsylate with no statistically significant differences observed between treatment groups. In particular the 90% confidence intervals for C_{max} and $AUC_{(0-144)}$ for the test drug/comparator ratios were 0.891 – 1.118 and 0.955 – 1.248 respectively and within the acceptance interval of 80-125% for bioequivalence. The results obtained in this study demonstrated that amlodipine camsylate 5 mg tablets were bioequivalent to amlodipine besylate 5 mg tablets.

IVa. Mechanism of Action

COZAAR XQ

COZAAR XQ combines two agents with complementary mechanisms of action to improve blood pressure control in hypertensive patients: losartan potassium, an angiotensin II receptor blocker (ARB), and amlodipine, a calcium channel blocker (CCB). Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Losartan

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. Angiotensin II bindsto the AT_1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle
cell proliferation. A second angiotensin II receptor has been identified as the AT_2 receptor subtype, but it plays no known role in cardiovascular homeostasis.

Losartan is a potent, synthetic, orally active compound. Based on binding and pharmacological bioassays, it binds selectively to the AT_1 receptor. *In vitro* and *in vivo*,

both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis. In contrast to some peptide antagonists of angiotensin II, losartan has no agonist effects.

Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of edema (losartan 1.7%, placebo 1.9%), are not associated with losartan.

Amlodipine

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

IVb. Pharmacokinetics

IVlb-1. 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 drug was administered with a standardized meal.

Amlodipine

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been

estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food.

IVb-2. 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.

Amlodipine

Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasmaproteins in hypertensive patients.

IVb-3. Metabolism

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-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.

Amlodipine

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

IVb-4. 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-labeled losartan in man, about 35% of radioactivity is recoveredin the urine and 58% in the feces. Following an intravenous dose of ^{14}C-labeled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the feces.

Amlodipine

Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

IVb-5. Characteristics in Patients

COZAAR XQ

COZAAR XQ has not been studied in any special populations, due to the well known nature of losartan and amlodipine. Caution is advised for losartan in renal and hepatic impairment, and is contraindicated in breast feeding. No formal studies have been performed in either the elderly or children. For amlodipine caution is advised in hepatic impairment, and amlodipine is contraindicated in unstable cardiovascular disease and pregnancy/lactation.

Losartan

The plasma concentrations of losartan and its active metabolite observed in elderly malehypertensives 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 10mL/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.

Amlodipine

The pharmacokinetics of amlodipine are not significantly influenced by renal

impairment.Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

IVc. Pharmacodynamics

COZAAR XQ

COZAAR XQ has been shown to be effective in lowering blood pressure. Both losartan and amlodipine lower blood pressure by reducing peripheral resistance. Calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms.

Losartan

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 AT_1, 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'sspecific 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.

Amlodipine

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood

pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105– 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted ina decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

IVd. Clinical Studies

The antihypertensive efficacy of COZAAR XQ was demonstrated in 3 controlled studies involving 646 patients with essential hypertension, 325 of whom were treated with COZAAR XQ for 8 weeks. The primary efficacy variable in all studies was change from baseline in sitDBP at endpoint. Secondary variables were change in sitSBP and responder rates. Clinically significant changes in sitDBP at 8 weeks (the primary endpoint) were demonstrated with COZAAR XQ versus monotherapy (losartan or amlodipine) in the studies performed.

In a double-blind, dose-finding study, a total of 320 patients with mild-to-moderate hypertension received treatments of four combinations of amlodipine and losartan (5/50, 5/100, 10/50 and 10/100 mg) or amlodipine alone (5, 10 mg) or losartan alone (50, 100

mg). All doses were initiated at the randomized dose. At week 8, the combination treatments of COZAAR XQ 5/50 and 5/100 were statistically significantly superior to their monotherapy components in reduction of sitDBP and sitSBP.

Table 2. Effect of COZAAR XQ on Sit DBP and Sit SBP at 8 Weeks

	Losartan 50 mg	Losartan 100 mg	Amlodipine 5 mg	Amlodipine 10 mg	COZAAR XQ 5/50 mg	COZAAR XQ 5/100 mg	COZAAR XQ 10/50 mg	COZAAR XQ 10/100 mg
Sit DBP Change (from baseline) *	-7.0±8.6 mmHg	-10.5±8.7 mmHg	-11.7±8.2 mmHg	-16.4±7.6 mmHg	-15.6±8.3 mmHg	-16.1±7.6 mmHg	-20.8±6.9 mmHg	-18.3±5.0 mmHg
Sit SBP Change (from baseline) *	-7.0±13.7 mmHg	-16.0±16.3 mmHg	-15.5±13.9 mmHg	-23.6±12.1 mmHg	-25.7±15.9 mmHg	-24.0±14.7 mmHg	-28.7±13.9 mmHg	-25.9±13.3 mmHg

* non-placebo adjusted

In a double-blind, active-controlled study, a total of 184 patients with mild to moderate hypertension who were not adequately controlled on amlodipine 5 mg received treatments of either COZAAR XQ 5/50 or amlodipine 10mg. At week 8, COZAAR XQ 5/50 showed similar incremental BP lowering effects to amlodipine 10mg.

Table 3. Additional BP Lowering of COZAAR XQ after 8 Weeks in Patients Uncontrolled on Amlodipine 5mg

	Switched to COZAAR XQ 5/50 mg	Titrated to Amlodipine 10 mg	Mean (95% CI) p-value
Sit DBP Change (from baseline)	-8.9 mmHg	-9.4 mmHg	-0.52 (-2.52,1.48) p=0.6095
Sit SBP Change (from baseline)	-12.2 mmHg	-13.4 mmHg	-1.17 (-4.42,2.08) p=0.4787
Response Rate* (total)	89.1%	87.9%	88.52% p=0.7960

* the rate of patients who achieved target blood pressure (sit SBP<140 mmHg or sit DBP<90 mm Hg), or sit SBP change more than 20 mmHg from baseline or sit DBPchange more than 10 mmHg from baseline

In a double-blind, active-controlled study, a total of 142 patients with mild to moderate hypertension who were not adequately controlled on losartan 100 mg were switched to COZAAR XQ 5/100 mg or remained on losartan 100 mg. At week 8, COZAAR XQ 5/100 mg showed superior incremental BP lowering effects to losartan 100 mg.

Table 4. Additional BP Lowering of COZAAR XQ after 8 Weeks in Patients Uncontrolled on Losartan 100mg

	Switched to COZAAR XQ 5/100mg	Stayed on Losartan 100 mg	Mean (95% CI) p-value
Sit DBP Change (from baseline)	-11.7mmHg	-3.2 mmHg	8.52 (6.03, 11.01) p<0.0001
Sit SBP Change (from baseline)	-13.4 mmHg	-3.4 mmHg	9.98 (6.05, 13.90) p<0.0001
Response Rate* (total)	90.0%	66.7%	78.2% p=0.0008

* the rate of patients who achieved target blood pressure (sit SBP<140mmHg or sit DBP<90mmHg), or sit SBP change more than 20 mmHg from baseline or sit DBP change more than 10 mmHg from baseline

V. INDICATIONS

COZAAR XQ (amlodipine camsylate/losartan potassium) is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled on either monotherapy.

VI. DOSAGE AND ADMINISTRATION

The recommended dose of COZAAR XQ is one tablet per day.

COZAAR XQ may be administered with or without food. It is recommended to take COZAARXQ with water.

COZAAR XQ may be administered with other antihypertensive agents.

Losartan is an effective treatment of hypertension in once daily doses of 50 mg to 100 mg while amlodipine is effective in doses of 5 mg to 10 mg as monotherapy. The maximum recommended dose of COZAAR XQ is 5 mg/100 mg.

A patient whose blood pressure is not adequately controlled with losartan alone or amlodipine alone may be switched to combination therapy with COZAAR XQ.

COZAAR XQ 5 mg/50 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or losartan 50 mg alone.

COZAAR XQ 5 mg/100 mg may be administered in patients whose blood pressure is not adequately controlled with losartan 100 mg or COZAAR XQ 5 mg/50 mg.

A patient co-administered with losartan and amlodipine may be switched to COZAAR XQ (fixed dose combination containing same dose of each ingredient) for compliance improvement.

Use in patients with renal impairment
No dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine

clearance 20-50 mL/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 mL/min) or patients on dialysis, administration of COZAAR XQ is not recommended.

Use in patients with intravascular volume depletion
For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg losartan once daily should be considered (see PRECAUTIONS). Since a 25 mg dose of losartan is not available with COZAAR XQ, this dose should be achieved with losartan monotherapy.

Use in patients with hepatic impairment
In cases where a lower dose of losartan (i.e. 25 mg once daily) is required for patients with a history of hepatic impairment, administration of COZAAR XQ is not recommended.

Use in the elderly
Because of decreased clearance in the elderly, amlodipine therapy should usually be initiated at 2.5 mg daily. Since a 2.5 mg dose of amlodipine is not available with COZAAR XQ, this dose should be achieved with amlodipine monotherapy.

Use in patients ≤18 years of age
Since safety and efficacy of COZAAR XQ in children ≤18 years of age has not been established, administration of COZAAR XQ is not recommended.

VII. CONTRAINDICATIONS

COZAAR XQ is contraindicated in patients who are hypersensitive to any component of this product.

COZAAR XQ should not be administered with aliskiren in patients with diabetes (see DRUG INTERACTIONS).

VIII. PRECAUTIONS

COZAAR XQ

Hypotension
In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics) or with severe aortic stenosis, symptomatic hypotension may occur. Intravascular volume depletion should be corrected prior to administration of COZAAR XQ, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION). Because of the gradual onset of action, acute hypotension is unlikely.

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose of losartan should be considered for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{½}$) is 56 hours in patients with impaired hepatic function, titrate slowly when administering amlodipine to patients with severe hepatic impairment.

Losartan

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 COZAAR XQ as soon as possible. (See PREGNANCY).

Hypersensitivity: Angioedema. (See SIDE EFFECTS.)

Electrolyte/Fluid Imbalance

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 and *Laboratory Test Findings*).

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

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.

Amlodipine

Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Use in Patients with Heart Failure

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic etiology, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

IX. PREGNANCY

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

Although there is no experience with the use of COZAAR XQ 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 COZAAR XQ 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 COZAAR XQ 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 COZAAR XQ, 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 HYZAAR for hypotension, oliguria, and hyperkalemia.

There are no adequate and well-controlled studies of amlodipine in pregnant women. The safety of amlodipine in pregnant women has not been established. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at the dose 50 times the maximum recommended human dose.

X. NURSING MOTHERS

While it is not known whether losartan or amlodipine is excreted in human milk, significant levels of amlodipine and/or losartan active metabolite were shown to be present in animal milk. Therefore, nursing mothers should not receive this drug.

XI. PEDIATRIC USE

Since safety and efficacy of COZAAR XQ in children ≤ 18 years of age has not been

established, administration of COZAAR XQ is not recommended.

Neonates with a history of *in utero* exposure to COZAAR XQ:
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.

XII. USE IN THE ELDERLY

In clinical studies there was no age-related difference in the efficacy or safety profile of losartan.Because of decreased clearance of amlodipine in the elderly, with a resulting increase of AUCof approximately 40–60% amlodipine therapy should usually be initiated at 2.5 mg daily. Since a
2.5 mg dose of amlodipine is not available with COZAAR XQ, this dose should be achieved with amlodipine monotherapy.

XIII. DRUG INTERACTIONS

COZAAR XQ

No drug interaction studies have been conducted with COZAAR XQ and other drugs, although studies have been conducted with the individual losartan and amlodipine components, asdescribed below.

Losartan

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 drugs that may increase serum potassium (e.g., trimethoprim-containing products) may lead to increases 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. Closely monitor blood pressure, renal function, and electrolytes in patients on COZAAR XQ and other agents that affect the RAAS. Do not co-administer aliskiren with COZAAR XQ in patients with diabetes. Avoid use of aliskiren with COZAAR XQ 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 COZAAR XQ.

Amlodipine In Vitro Data
In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Cimetidine
Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit Juice
Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Magnesium and Aluminum Hydroxide Antacid
Co-administration of a magnesium and aluminum hydroxide antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil
A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin
Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin
Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (Alcohol)
Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin
Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

CYP3A4 Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 1.6-fold increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers
No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

Drug/Laboratory Test
Interactions None
known.

XIV. SIDE EFFECTS

COZAAR XQ

The safety of COZAAR XQ has been evaluated in 325 patients treated with amlodipine/losartan combination therapy among 646 essential hypertension patients in 3 clinical trials (study 201, study 301 and study 302) for 8 weeks. Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100, <1/10);
uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Table 1. The treatment-related* adverse events

System Organ Class	Frequency	Adverse Event
Nervous system disorders	Common	Dizziness, Headache
	Uncommon	Somnolence
General disorders and administration site conditions	Uncommon	Asthenia, Chest discomfort, Chest pain, Early satiety, Edema peripheral, Pitting edema
Gastrointestinal disorders	Uncommon	Abdominal discomfort, Dyspepsia, Nausea, Reflux oesophagitis
Skin and subcutaneous tissue disorders	Uncommon	Pruritus (generalized), Urticaria (generalized)
Cardiac disorders	Uncommon	Palpitation

Vascular disorders	Uncommon	Flushing, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Sensory organ disorders	Uncommon	Vertigo
Renal and urinary disorder	Uncommon	Pollakiuria

* The adverse experiences to be definitely related, probably related or possibly related to drug or uncertain considered by investigators.

Additional information for each active ingredient
The following adverse reactions have been reported with the components of COZAAR XQ.

Losartan

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Losartan has been found to be generally well-tolerated in controlled clinical trials for hypertension; side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with losartan was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in one percent or more of patients treated with losartan. In addition, dose related orthostatic effects were seen in less than one percent of patients. Rarely, rash was reported, although the incidence in controlled clinical trials was less than placebo.

In these double-blind controlled clinical trials for essential hypertension, the following adverse experiences reported with losartan occurred in ≥1 percent of patients, regardless of drug relationship:

	Losartan (n=2085)	**Placebo (n=535)**
Body as a Whole		
Abdominal pain	1.7	1.7
Asthenia/fatigue	3.8	3.9
Chest pain	1.1	2.6
Edema/swelling	1.7	1.9
Cardiovascular		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
Digestive		
Diarrhea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
Musculoskeletal		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
Nervous/Psychiatric		

Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
Respiratory		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory infection	6.5	5.6

Losartan 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.

In that study, among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with losartan as compared to atenolol (242 patients versus 320 patients,respectively, $p<0.001$). Because there was no placebo group included in the study, it is not known if this represents a beneficial effect of losartan or an adverse effect of atenolol.

Losartan 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 PRECAUTIONS, Hypotension and Electrolyte/Fluid Imbalance).

The following additional adverse reactions have been reported in postmarketing 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. Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists including few cases with losartan. Vasculitis, including Henoch-Schonlein 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.

Amlodipine besylate

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Amlodipine besylate has been evaluated for safety in more than 11,000 patients in

worldwide clinical trials. In general, treatment with amlodipine besylate was well-tolerated at doses up to10 mg daily. Most adverse reactions reported during therapy with amlodipine besylate were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine besylate (N=1730) at doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine besylate due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects that occurred in a dose related manner are as follows:

Adverse Event	2.5 mg	5.0 mg	10.0 mg	Placebo
	N=275	N=296	N=268	N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences that were not clearly dose related but were reported with anincidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies		
	Amlodipine besylate (%)	Placebo (%)
	(N=1730)	(N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine besylate treatment as shown in the following table:

	Amlodipine besylate		Placebo	
Adverse Event	Male=%	Female=%	Male=%	Female=%
	(N=1218)	(N=512)	(N=914)	(N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or

under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, posturaldizziness, postural hypotension, vasculitis.
Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.
Gastrointestinal: anorexia, constipation, dyspepsia[1], dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.
General: allergic reaction, asthenia[1], back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
Musculoskeletal System: arthralgia, arthrosis, muscle cramps[1], myalgia.
Psychiatric: sexual dysfunction (male[1] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory System: dyspnea[1], epistaxis.
Skin and Appendages: angioedema, erythema multiforme, pruritus[1], rash[1], rash erythematous, rash maculopapular.
Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.
Urinary System: micturition frequency, micturition disorder, nocturia.
Autonomic Nervous System: dry mouth, sweating increased. Metabolic and Nutritional: hyperglycemia, thirst.
Hemopoietic: leukopenia, purpura, thrombocytopenia.

[1] These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

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

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine besylate.

Amlodipine besylate has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

XIVa. Laboratory Test Findings

COZAAR XQ

Slowed heart rate was observed in some patients 8 weeks after administration of losartan/amlodipine, but the change in heart rate was not clinically significant.

Increased blood creatinine and increased hepatic enzyme were reported in some patients but specific laboratory monitoring is not required.

Losartan

In controlled clinical trials for essential hypertension, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR. Hyperkalemia (serum potassium >5.5 mEq/L) occurred in 1.5% of patients in the hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with proteinuria, 9.9% of patients treated with COZAAR and 3.4% of patients treated with placebo developed hyperkalemia (see PRECAUTIONS, Hypotension and Electrolyte/Fluid Imbalance). Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

Amlodipine

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

XV. OVERDOSAGE

COZAAR XQ

There are no data available in regard to overdosage of COZAAR XQ in humans. The overdose on each ingredient of amlodipine and losartan are described.

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.

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Non-cardiogenic pulmonary edema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support, or may result in a fatal outcome. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

XVI. APPEARANCE & AVAILABILITY

COZAAR XQ 5/50MG: white, modified capsule shaped, film-coated tablet, debossed with ‘222’ on one side and plain on the other side.

COZAAR XQ 5/100mg: pink, modified capsule shaped, film-coated tablet, debossed with ‘331’ on one side and the plain on the other side.

COZAAR XQ 5/50MG and COZAAR XQ 5/100mg are available in blister packs of 30's.

XVII. STORAGE

Store at temperatures below 30°C (86°F). Store in the original package. Protect from moisture.

XVIII. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies of the effects of COZAAR XQ on the ability to drive and operate machines

have been performed. However, certain side effects that have been reported with COZAAR XQ may affect some patients' ability to drive or operate machinery. Individual responses to COZAAR XQ may vary. (See SIDE EFFECTS.)

XIX. ANIMAL TOXICOLOGY

XIXa. Acute Toxicity

No single-dose toxicity studies have been conducted with COZAAR XQ.

Losartan

The oral LD_{50} of losartan potassium in male mice is 2248 mg/kg (6744 mg/m^2) (1124 times the maximum recommended human daily dose). Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m^2) and 2000 mg/kg (11,800 mg/m^2) (500 and 1000 times** the maximum recommended daily human dose), respectively.

Amlodipine

In single-dose studies, the approximate lethal oral dose of amlodipine camsylate was 150 mg/kg in rats and 10 mg/kg in dogs.

** Based on a patient weight of 50 kg.

XIXb. Chronic Toxicity

COZAAR XQ

Repeated dose toxicity studies of up to 13 weeks with the amlodipine camsylate/losartan potassium combination at a ratio of 1:20 (the highest ratio used in clinical studies) at doses up to 15/300 mg/kg in rats and 2/40 mg/kg in dogs did not result in increase in severity of toxicity or additional toxicities over that observed with the individual substances administered at the highest dose used in the combination. There were no findings that would preclude administration of COZAAR XQ at the therapeutic dosage level.

Losartan

The toxic potential of losartan potassium was evaluated in a series of repeated dose oraltoxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

XIXc. Carcinogenesis

No carcinogenicity studies have been conducted with COZAAR XQ.

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.

Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showedno evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about twice the maximum recommended human dose.

XIXd. Mutagenesis

No mutagenicity studies have been conducted with COZAAR XQ.

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/m^2) (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.

Amlodipine

Mutagenicity studies conducted with amlodipine maleate and amlodipine camsylate revealed no drug related effects at either the gene or chromosome level.

XIXe. Reproduction

No individual studies have been conducted with COZAAR XQ.

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.

Amlodipine

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose*** of 10 mg/day on a mg/m^2 basis).

*** Based on patient weight of 50 kg.

XIXf. Development

No individual studies have been conducted with COZAAR XQ.

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 drug exposure in late gestation and during lactation.

Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the maximum recommended human dose [MRHD] of 10 mg amlodipine on a mg/m^2 basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg.) However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) for rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women.

XX. SHELF LIFE

Please refer to the expiry date on the outer carton.

XXI. MANUFACTURED BY:

Hanmi Pharm. Co., Ltd.
214, Muha-ro, Paltan-myeon,

Hwaseong-si, Gyeonggi-do,
Korea.

XXII. PRODUCT REGISTRATION HOLDER:

ORGANON MALAYSIA SDN. BHD.
3A-08-02, Level 8, Corporate Tower 3A,
Pavilion Damansara Heights,
No. 3, Jalan Damanlela
50490 Kuala Lumpur, Malaysia.

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