**Summary of the Product Characteristics**

**UNIZAR FORTE**

**(Losartan Potassium, Amlodipine & Hydrochlorothiazide Tablets)**

## 1. NAME OF THE MEDICINAL PRODUCT

**UNIZAR FORTE**

(Losartan Potassium, Amlodipine & Hydrochlorothiazide Tablets)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Losartan Potassium USP.....50 mg

Amlodipine Besylate USP

Eq.to Amlodipine.....5 mg

Hydrochlorothiazide USP.....12.5 mg

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

A Peach coloured, heart shaped biconvex, film- coated, tablet having plain on both sides of the tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

UNIZAR FORTE is indicated for the treatment of essential hypertension. **Adult:** Per tablet contains amlodipine 5 mg and losartan potassium 50 mg: Initial: 1 tablet once daily; may increase to 2 tablets daily if the BP control is inadequate after 1-2 wk.
UNIZAR FORTE may be used in patients whose blood pressure is not adequately controlled on either monotherapy.

## 4.2 Posology and method of administration

The recommended dose of UNIZAR FORTE is one tablet per day.
UNIZAR FORTE may be administered with or without food. It is recommended to take UNIZAR FORTE with water. UNIZAR FORTE 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 UNIZAR FORTE is 100 mg/5 mg. A patient whose blood pressure is not adequately controlled with losartan alone or amlodipine alone may be switched to combination therapy with UNIZAR FORTE.

UNIZAR FORTE 50 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or losartan 50 mg alone. UNIZAR FORTE 100 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled with losartan 100 mg or UNIZAR FORTE. A patient co-administered with losartan and amlodipine may be switched to UNIZAR FORTE (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 UNIZAR FORTE 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 . Since a 25 mg dose of losartan is not available with UNIZAR FORTE 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 UNIZAR FORTE 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 UNIZAR FORTE, this dose should be achieved with amlodipine monotherapy.

**Use in adolescents and children**

Since safety and efficacy of UNIZAR FORTE in children ≤18 years of age has not been established, administration of UNIZAR FORTE is not recommended.

## 4.3 Contraindications

Known hypersensitivity. Avoid concomitant K supplements. Pregnancy. Special Precautions Impaired hepatic or renal function, CHF, sick-sinus syndrome, severe ventricular dysfunction, hypertrophic cardiomyopathy. Elderly, children. Lactation. Volume-depleted patients; patients on diuretics and salt restriction; renal artery stenosis. Monitor serum K concentration.

## 4.4 Special warnings and precautions for use

UNIZAR FORTE 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 UNIZAR FORTE, or a lower starting dose should be used. 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 and CLINICAL PHARMACOLOGY, Pharmacokinetics. Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t1/2) is 56 hours in patients with impaired hepatic function, titrate slowly when administering amlodipine to patients with severe hepatic impairment.

**Losartan**
Hypersensitivity: Angioedema. 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.
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.

Hydrochlorothiazide**:** may make you more sensitive to the sun. Avoid prolonged sun exposure, tanning booths or sunlamps. Use a sunscreen and wear protective clothing when outdoors.Kidney function declines as you grow older. This medication is removed by the kidneys; therefore, elderly people may be a greater risk for dizziness while using this drug.This medication is not recommended for use during pregnancy due to the risk for harm to an unborn baby. Consult your

doctor for more details. (See also Warning section.) Hydrochlorothiazide passes into breast milk. Breast-feeding is not recommended due to the potential harm to the nursing infant. Consult your doctor before breast-feeding. This drug can cause serious (possibly fatal) harm to an unborn baby if used during pregnancy. Therefore, it is important to prevent pregnancy while taking this medication. Consult your doctor for more details and to discuss the use of reliable forms of birth control while taking this medication. If you are planning pregnancy, become pregnant, or think you may be pregnant, contact your doctor immediately.

## 4.5 Interaction with other medicinal products and other forms of interaction

**Losartan:** Concurrent use with NSAIDs may further worsen renal function. Cimetidine may increase the AUC of losartan by about 18%. Phenobarbital and other enzyme inducers may decrease levels of losartan and its active metabolite. Ketoconazole inhibits the conversion of losartan to its active metabolite. Concurrent use with potassium-sparing diuretics or potassium supplements or salt substitutes containing potassium may increase serum potassium levels. Reduces lithium excretion; monitor lithium levels if used together.

**Potentially Fatal:** Increased cyclosporine levels. Risk of lithium toxicity with losartan. Hypotensive effect of losartan potentiated by diuretics and other antihypertensives. Risk of hyperkalaemia increases with concomitant ACE inhibitors, potassium-sparing diuretics and K supplements.

**Amlodipine:** Increased metabolism with rifampin. Reduced hypotensive effect with calcium. Potentiates effects of thiazide diuretics and ACE inhibitors. Avoid combination with β-blockers in patients with markedly impaired left ventricular function.

**Hydrochlorothiazide:** The classifications below are a general guideline only. It is difficult to determine the relevance of a particular drug interaction to any individual given the large number of variables.

**Major:** Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.

**Moderate:** Moderately clinically significant. Usually avoid combinations; use it only under special circumstances.

**Minor:** Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.

## 4.6 Pregnancy and lactation

**Hydrochlorothiazide / losartan Pregnancy Warnings**

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered during pregnancy. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme (ACE) inhibitors. A committee of the National Institutes of Health has recommended that these drugs be avoided during pregnancy. When pregnancy is detected or expected, hydrochlorothiazide-losartan should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the use of these drugs. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of hydrochlorothiazide-losartan as soon as possible. There are significant warnings against the use of thiazides during pregnancy. The Collaborative Perinatal Project monitored 50,282 mother-child pairs, of whom 233 were exposed to thiazide or related diuretics during the first trimester. An increased risk of malformations was found for thiazide diuretics. Use of thiazides after the first trimester does not seem to carry this risk. Thiazide diuretics may, however pose metabolic risks to the mother and fetus (hyponatremia, hypokalemia, thrombocytopenia, hyperglycemia), and may have a direct effect on smooth muscle, resulting in inhibition of labor. Data from the Michigan Medicaid Birth Defects Study has revealed an association between the use of HCTZ and congenital abnormalities (written communication, Franz Rosa, MD, Food and Drug Administration, 1994). This was a retrospective study of 229,101 completed pregnancies between 1985 and 1992, of which 567 were exposed to HCTZ at some time during the first trimester and 1,173 were exposed to the drug at

any time during pregnancy. Of the 567 pregnancies, there were 24 total and 7 cardiovascular birth defects (22 and 6 were expected, respectively). There were no observations of cleft palate, spina bifida, limb reduction, or hypospadias. The one instance of polydactyly did not achieve statistical significance. These data are consistent with an association between the use of HCTZ and birth defects, although other factors, including any underlying disease(s) of the mother were not accounted for. Cases of neonatal thrombocytopenia associated with antepartum administration of thiazide diuretics have been reported.

Hydrochlorothiazide-losartan has been assigned to pregnancy category C (first trimester) and D (second and third trimesters) by the FDA. Animal data have shown that the use of losartan produces adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses of losartan associated with these effects exceeded 25 mg/kg/day (approximately 3 times the maximum recommended human dose of 100 mg, on a mg/m2 basis). These findings are attributed to drug exposure in late gestation and during lactation. There are no controlled data in human pregnancy. The manufacturer states that when used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. Retrospective reviews have shown an increased risk of malformations associated with thiazide diuretics. Hydrochlorothiazide-losartan is considered contraindicated during pregnancy.

Hydrochlorothiazide / losartan Breastfeeding Warnings

There are no data on the excretion of losartan into human milk. Losartan and its active metabolite are excreted into rat milk. Hydrochlorothiazide is secreted into human milk in low concentrations. 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.

**Amlodipine:**

Fetal Risk Summary

Amlodipine is a calcium channel-blocking agent used in the treatment of hypertension and angina. The drug is not teratogenic or embryotoxic in rats and rabbits given doses up to 8 and 23 times, respectively, the maximum recommended human dose (MRHD) on a body surface area basis during their respective periods of major organogenesis (1). However, rats administered 8 times the MRHD for 14 days before mating and throughout gestation had a significant decrease in litter size (by about 50%), a significant increase in intrauterine deaths (about 5-fold), and prolonged labor and gestation (1). This dose, however, had no effect on fertility in the rat.

No reports describing the placental transfer of amlodipine in humans have been located. The molecular weight (about 567 for the besylate salt) is low enough, however, that passage to the fetus should be expected.

No reports on the use of amlodipine in human pregnancy have been located.

Breast Feeding Summary

No reports describing the use of amlodipine during human lactation have been located. The molecular weight (about 567 for the besylate salt) is low enough, however, that excretion into breast milk should be expected. The effect of the drug on a nursing effect is unknown.

## 4.7 Effects on ability to drive and use machines

No such effects.

## 4.8 Overdose:

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 tablets 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/ m2 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 tablets is highly protein bound, hemodialysis is not likely to be of benefit.

Losartan and Hydrochlorothiazide Losartan Potassium
Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/ m2 basis.
Limited data are available in regard to over dosage in humans. The most likely manifestation of over dosage 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 its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. The most common signs and symptoms observed are those caused by

electrolyte depletion (hypokalemia, hypochloremic, hyponatreamia) 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.

**Reporting of suspected adverse reactions:** Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

### 4.9 Overdose

**Symptoms**

Bradycardia, dehydration, electrolyte depletion (eg, hypochloremia, hypokalemia, hyponatremia), hypotension, tachycardia.

If overdose is suspected, contact your local poison control center or emergency room immediately. US residents can call the US national poison hotline at 1-800-222-1222. Canadian residents should call their local poison control center directly. Symptoms of overdose may include unusually fast or slow heartbeat, severe dizziness or fainting.

Symptoms may include fainting; flushing; severe or persistent dizziness or light-headedness; symptoms of blood electrolyte problems (eg, confusion; irregular heartbeat; mental or mood changes; muscle pain, weakness, or cramping; seizures; sluggishness); symptoms of dehydration (eg, drowsiness; dry eyes; fast heartbeat; nausea; restlessness; unusual thirst, tiredness, or weakness; vomiting).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties ATC code:

**Losartan:** C09CA01-Belongs to the class of angiotensin II antagonists. Used in the treatment of cardiovascular disease.

**Amlodipine:** C08CA01-Belongs to the class of selective dihydropyridine derivative calcium-channel blockers with mainly vascular effects. Used in the treatment of cardiovascular diseases. **Hydrochlorothiazide:** C03AA03

UNIZAR FORTE 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 Mlead 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.

**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 in a 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: amlodpine 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.

**Hydrochlorothiazideis** a diuretic (water pill) used for treating high blood pressure (hypertension) and accumulation of fluid. It works by blocking salt and fluid reabsorption in the kidneys, causing an increased amount of urine containing salt (diuresis). The mechanism of its action in lowering high blood pressure is not well understood. The combination of losartan and reduces blood pressure better than either drug alone. Losartan increases potassium levels while reduces potassium levels; the combination of both drugs has less effect on potassium levels.

**5.2 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 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.

**Hydrochlorothiazide** is variably but fairly rapidly absorbed from the gastrointestinal tract. Bio-availability of hydrochlorothiazide after oral administration is approximately 60 to 80 per cent. Peak plasma level occurs after 1 to 2 hours.

**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 plasma proteins in hypertensive patients.

**Hydrochlorothiazide** is widely distributed in body tissue and its volume of distribution following oral administration corresponds to 0.83 L/Kg

**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 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.

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.

**Hydrochlorothiazide** is not modified by organic biochemical processes.

**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 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.

**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.

**Characteristics in Patients**

UNIZAR FORTE 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 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.

**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.

Elimination of hydrochlorothiazide is mainly due to renal clearance that occurs in about 320 mg/min. It is excreted unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and appears in breast milk. Total systemic clearance of drug from the plasma is 4.9 mL/min/kg , decreasing in patients with uremia or congestive heart failure.

## 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Fetal 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 fetal and neonatal effects, including renal toxicity and fetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

| Sr. No. | Ingredients | Specification |
|---|---|---|
| 1 | Lactose | BP |
| 2 | Microcrystalline cellulose | BP |
| 3 | Hydroxypropylcellulose | BP |
| 4 | Low-Substituted Hydroxypropyl Cellulose | USP |
| 5 | Purified Water | BP |
| 6 | Microcrystalline cellulose | BP |
| 7 | Sodium starch glycolate (Type A) | BP |
| 8 | Colloidal Anhydrous Silica | BP |
| 9 | Magnesium Stearate | BP |
| 10 | Crospovidone | BP |
| 11 | Sodium Lauryl Sulfate | BP |
| 12 | Hypromellose | BP |
| 13 | Isopropyl Alcohol | BP |
| 14 | Dichloromethane | BP |
| 15 | Purified Talc | BP |
| 16 | Titanium Dioxide | BP |
| 17 | Diethyl phthalate | BP |
| 18 | Ferric oxide Red | IHS |

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Store below 30°C, Protect from light & moisture.

## 6.5 Nature and contents of container

A) 1) 10 Tablets blister packed in Printed Aluminium Foil and Clear PVC Film.
2) 3 blisters are packed in carton with leaflet.

B) 1) 10 Tablets blister packed in Printed Aluminium Foil and Clear PVC Film.
2) 1 blisters are packed in carton with leaflet.

## 6.6 Special precautions for disposal

No special requirements

## 7.MARKETING AUTHORISATION HOLDER

MEDISEL (KENYA) LIMITED
Factory Street,
P.O.BOX 540,
Thika,
Kenya.

## 8.MARKETING AUTHORISATION NUMBER(S)

H2016/CTD2818/007/R1

## 9.DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

April 2026

## 10. DATE OF REVISION OF THE TEXT