CRESAR PLUS Tablets (Telmisartan + Amlodipine + Hydrochlorothiazide)

**Black Box Warning**

**Fetal Toxicity**

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

**Composition**

CRESAR PLUS

Each uncoated tablet contains Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorothiazide 12.5 mg

**Dosage Form**

Tablet

**Description**

CRESAR PLUS is a fixed dose combination containing telmisartan, a non-peptide angiotensin II receptor (type AT₁) antagonist; amlodipine, a dihydropyridine calcium antagonist and hydrochlorothiazide, a thiazide diuretic. This combination lowers the BP through complementary mechanisms, each working at a separate site and blocking different effector pathways in hypertensive patients.

**Pharmacology**

**Pharmacodynamics**

The active ingredients of CRESAR PLUS target three separate mechanisms involved in blood pressure (BP) regulation. Specifically, amlodipine blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells; telmisartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells; and hydrochlorothiazide directly promotes the excretion of sodium and chloride in the kidney leading to reductions in intravascular volume.

**Telmisartan**

Telmisartan is a non-peptide angiotensin II receptor blocker (ARB). Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS), with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan 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, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the
pathways for angiotensin II synthesis. There is also an AT$_2$ receptor found in many tissues, but AT$_2$ is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (> 3,000 fold) for the AT$_1$ receptor than for the AT$_2$ receptor. Blockade of the RAS with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity (PRA) and angiotensin II circulating levels do not overcome the effect of telmisartan on BP.

The antihypertensive effects of telmisartan have been studied in six placebo-controlled clinical trials including a total of 1773 patients with mild to moderate hypertension (diastolic BP of 95 to 114 mmHg), 1031 of whom were treated with telmisartan. Following once-daily administration of telmisartan, the magnitude of BP reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in BP. The onset of antihypertensive activity occurs within 3 hours, with a maximal reduction by approximately 4 weeks. At doses of 20, 40, and 80 mg, the antihypertensive effect of once-daily administration of telmisartan was maintained for the full 24-hour dose interval.

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours. Plasma concentration of angiotensin II and PRA increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate (GFR), filtration fraction, renovascular resistance, or creatinine clearance.

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 BP. Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing BPs. These decreases in BP 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 BP 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 BPs 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 BP with amlodipine is also correlated with the height of pre-treatment 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 BPs (+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 GFR 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 humans, even when co-administered with beta-blockers to humans. Similar findings, however, have been observed in normals or well-compensated patients having heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular (AV) conduction in intact animals or humans. 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.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in PRA, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an ARB tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is not fully understood.

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics

Absorption

Telmisartan

Following oral administration, peak concentrations ($C_{max}$) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. Telmisartan/hydrochlorothiazide/amlodipine can be administered with or without food. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg, the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally
administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

**Amlodipine**

Peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food.

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

**Hydrochlorothiazide**

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. Following oral administration of telmisartan/hydrochlorothiazide/amlodipine, peak concentrations of hydrochlorothiazide are reached in approximately 1.0-3.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60%.

**Distribution**

**Telmisartan**

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and (alpha)-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

**Amlodipine**

The apparent volume of distribution of amlodipine is 21 L/kg. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

**Hydrochlorothiazide**

Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.83-1.14 l/kg. Hydrochlorothiazide crosses the placenta, but not the blood-brain barrier and is excreted in breast milk.

**Metabolism and Elimination**

**Telmisartan**

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (more than 97%) was eliminated unchanged in the feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Total plasma clearance of telmisartan is more than 800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

**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**

Hydrochlorothiazide is not metabolized, but is eliminated rapidly by the kidneys.

Hydrochlorothiazide is excreted almost entirely as unchanged substance in urine. About 60% of the oral dose is eliminated within 48 hours. Renal clearance is about 250-300 ml/min. The terminal elimination half-life of
Special Populations

Geriatric Populations
The pharmacokinetics of telmisartan does not differ between the elderly and those younger than 65 years. However, elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40%-60%; therefore a lower initial dose of amlodipine may be required.

Pediatric Populations
Telmisartan pharmacokinetics has not been investigated in patients < 18 years of age. The effect of amlodipine on BP in patients < 6 years of age is not known.

Gender
Population pharmacokinetic analysis indicated that gender had no effect on the clearance of amlodipine. Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in BP response or in the incidence of orthostatic hypotension were found in women; no dosage adjustment is necessary. Female patients had approximately 20% lower clearances of hydrochlorothiazide than male patients.

Renal Impairment
No dosage adjustment of telmisartan is necessary in patients with decreased renal function as it is not removed from blood by hemofiltration. The pharmacokinetics of amlodipine is not significantly influenced by renal impairment, thus patients with renal failure may receive the usual initial dose. In patients with impaired renal function the rate of hydrochlorothiazide elimination is reduced. In a typical study in patients with a mean creatinine clearance of 90 ml/min the elimination half-life of hydrochlorothiazide was increased. In functionally anephric patients the elimination half-life is about 34 hours.

Hepatic Impairment
As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic impairment can be expected to have reduced clearance. In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required.

Indications
CRESAR PLUS is indicated for the treatment of hypertension.
This fixed combination drug is not indicated for the initial therapy of hypertension.

Dosage And Administration

General Considerations
The usual dose is one tablet once daily. The dosage may be increased to two tablets once daily after two weeks of therapy. The maximum recommended dose of CRESAR PLUS is 10/80/25 mg.
CRESAR PLUS may be administered with or without food.
Initiating therapy with CRESAR PLUS is not recommended in patients ≥ 75 years old, as these patients should start amlodipine at 2.5 mg.
Add-on/ Switch Therapy

CRESAR PLUS may be used for patients not adequately controlled on any two of the following antihypertensive classes: calcium channel blockers, ARBs, and diuretics.
A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of CRESAR PLUS may be switched to CRESAR PLUS containing a lower dose of that component to achieve similar BP reductions.

Replacement Therapy

CRESAR PLUS may be substituted for the individually titrated components.

Specific Populations

Renal Impairment: No initial dosage adjustment is required for patients with mild or moderate renal impairment. Safety and effectiveness of CRESAR PLUS in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) have not been established. In patients with severe renal impairment, CRESAR PLUS tablets are not recommended.

Hepatic Impairment: CRESAR PLUS is not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic impairment should have treatment started with CRESAR PLUS under close medical supervision.

Patients 75 Years of Age and Older: Patients ≥ 75 years of age should start amlodipine at 2.5 mg, therefore initial therapy with CRESAR PLUS is not recommended in patients > 75 years old.

Pediatric Use: The safety and effectiveness of CRESAR PLUS in pediatric patients have not been established.

Contraindications

Telmisartan /hydrochlorothiazide/amlodipine is contraindicated in patients with known hypersensitivity to telmisartan, hydrochlorothiazide or amlodipine or any other component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Cholestasis and biliary obstructive disorders.

Severe hepatic impairment.

Severe renal impairment (creatinine clearance < 30 ml/min).

Refractory hypokalemia, hypercalcemia.

Second and third trimesters of pregnancy

Biliary obstructive disorders and severe hepatic impairment

Shock (including cardiogenic shock)

Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)

Hemodynamically unstable heart failure after acute myocardial infarction

Do not co-administer aliskiren with telmisartan /hydrochlorothiazide/amlodipine in patients with diabetes.

Warnings And Precautions

General

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated angle-closure glaucoma can lead to permanent vision loss. The
primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

**Hypotension in Volume- or Salt-Depleted Patients**

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initialization of treatment with telmisartan/hydrochlorothiazide/amlodipine. Correct volume or salt depletion prior to the administration of telmisartan/hydrochlorothiazide/amlodipine.

**Increased Angina and/or Myocardial Infarction**

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

**Hypersensitivity Reaction**

Hypersensitivity reactions to telmisartan/hydrochlorothiazide/amlodipine may occur in patients with or without a history of allergy or bronchial asthma to hydrochlorothiazide, but are more likely in patients with such a history.

**Systemic Lupus Erythematosus**

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

**Serum Electrolytes**

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalemia, hyponatremia and hypochloremia alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, asthenia, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

**Hypokalemia**

Although hypokalemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalemia. The risk of hypokalemia is greater in patients with cirrhosis of liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or Adrenocorticotropic hormone (ACTH).

**Hyperkalemia**

Conversely, due to the antagonism of the \( \text{AT}_1 \) receptors by the telmisartan component of telmisartan/hydrochlorothiazide/amlodipine, hyperkalemia might occur. Although clinically significant hyperkalemia has not been documented with telmisartan/hydrochlorothiazide/amlodipine, risk factors for the development of hyperkalemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with telmisartan/hydrochlorothiazide/amlodipine.

**Hyponatremia and hypochloremia alkalosis**

There is no evidence that telmisartan/hydrochlorothiazide/amlodipine would reduce or prevent diuretic-induced hyponatremia. Chloride deficit is generally mild and usually does not require treatment.

**Hypercalcemia**

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

**Hypomagnesaemia**

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.
Ethnic differences
As with all other ARBs, telmisartan is apparently less effective in lowering BP in black patients than in non-blacks, possibly because of higher prevalence of low renin states in the black hypertensive population.

Dual Blockade of the RAS
Dual blockade of the RAS with ARBs, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomized them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit on the composite endpoint of cardiovascular death, myocardial infarction, stroke and heart failure hospitalization compared to monotherapy, but experienced an increased incidence of clinically important renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Co-administration of telmisartan and ramipril increases the exposure to both ramipril and ramiprilat by a factor of about 2. Concomitant use of telmisartan and ramipril is not recommended.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. Closely monitor BP, renal function and electrolytes in patients on telmisartan/hydrochlorothiazide/amlodipine and other agents that affect the RAS.

Do not co-administer aliskiren with telmisartan/hydrochlorothiazide/amlodipine in patients with diabetes. Avoid concomitant use of aliskiren with telmisartan/hydrochlorothiazide/amlodipine in patients with renal impairment (GFR<60 mL/min /1.73 m²).

Co-administration of telmisartan and ramipril increases the exposure to both ramipril and ramiprilat by a factor of about 2.

Hyperkalemia
Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Drug Interactions

**Aliskiren:** Do not co-administer aliskiren with telmisartan/hydrochlorothiazide/amlodipine in patients with diabetes. Avoid use of aliskiren with telmisartan/hydrochlorothiazide/amlodipine in patients with renal impairment.

**Alcohol, Barbiturates, or Narcotics:** Potentiation of orthostatic hypotension may occur.

**Antidiabetic Drugs (Oral Agents and Insulin):** Dosage adjustment of the antidiabetic drugs may be required.

**Cholestyramine and Colestipol Resins:** Absorption of telmisartan/hydrochlorothiazide/amlodipine is impaired in the presence of anionic exchange resins. Stagger the dosage of hydrochlorothiazide and the resin such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

**Corticosteroids, ACTH or Glycyrrhizin (found in liquorice):** Intensified electrolyte depletion, particularly hypokalemia can occur.

**CYP3A4 Inhibitors:** Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% 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 telmisartan/hydrochlorothiazide/amlodipine is co-administered with CYP3A4 inhibitors.
CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin, St. John’s Wort) on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of thiazide diuretics or ARBs, including telmisartan. Monitor lithium levels in patients receiving telmisartan/hydrochlorothiazide/amlodipine and lithium.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia favours the onset of digitalis-induced arrhythmia.

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Monitor digoxin levels in patients taking concomitant telmisartan/hydrochlorothiazide/amlodipine and digoxin.

Digitalis glycosides: Medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives): If these substances are to be prescribed with the telmisartan/hydrochlorothiazide/amlodipine combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium.

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporine or other medicinal products such as heparin sodium): If these medicinal products are to be prescribed with the telmisartan/hydrochlorothiazide/amlodipine combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the RAS, concomitant use of the above medicinal products may lead to increases in serum potassium and is, therefore, not recommended.

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when telmisartan/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes inducing medicinal products (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes.

Pressor Amines (eg, Norepinephrine): Co-administration of hydrochlorothiazide with pressor amine possibly decrease its response but not sufficiently to preclude their use.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ARB including telmisartan. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Lithium should not generally be given with thiazides.

Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of telmisartan decreases by 31% and 16% respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibility additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in
the presence of telmisartan. Concomitant use of telmisartan /hydrochlorothiazide/amlodipine and ramipril is not recommended.

**Skeletal Muscle Relaxants, Non-Depolarizing (eg. Tubocurarine):** Possible increased responsiveness to the muscle relaxant may occur on coadministration with hydrochlorothiazide.

**Simvastatin:** Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on telmisartan /hydrochlorothiazide/amlodipine to 20 mg daily.

**Medicinal products used in the treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol):** Dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide may increase the incidence of hypersensitivity reactions of allopurinol.

**Calcium salts:** Thiazide diuretics may increase serum calcium levels due to the decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

**Beta-blockers and diazoxide:** The hyperglycemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

**Anticholinergic agents (e.g. atropine, biperiden):** May increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

**Amantadine:** Thiazides may increase the risk of adverse effects caused by amantadine.

**Cytotoxic agents (e.g. cyclophosphamide, methotrexate):** Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects. Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics or antidepressants.

**Warfarin:** Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).

**Metformin:** Metformin should be used with precaution: risk of lactic acidosis induced by a possible functional renal failure linked to hydrochlorothiazide.

**Other Antihypertensive Drugs:** Telmisartan may increase the hypotensive effect of other antihypertensive agents. Clinical trial data has shown that dual blockade of the RAS through the combined use of ACE-inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAS-acting agent.

**Other Antihypertensive Drugs:** Additive effect or potentiation.

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):** In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ARBs, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ARBs, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors. In some patients, the administration of NSAIDs can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium sparing and thiazide diuretics. Therefore, when telmisartan/hydrochlorothiazide/amlodipine tablets and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. Also, renal function should be monitored periodically in patients receiving telmisartan/hydrochlorothiazide/amlodipine tablets and NSAID therapy.

**Other Drugs:** Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of
CYP2C19. Amlodipine has been safely administered with thiazide diuretics, beta-blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, NSAIDs, cimetidine, magnesium and aluminum hydroxide antacid, atorvastatin, sildenafil, ethanol antibiotics, and oral hypoglycemic drugs.

**Other**

As with any antihypertensive agent, excessive reduction of BP in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke

**Renal Impairment**

There are no studies of telmisartan/hydrochlorothiazide/amlodipine in patients with renal impairment. As a consequence of inhibiting the RAS, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the RAS, treatment with ACE inhibitors and ARBs has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan. In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. There has been no long-term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Avoid use of telmisartan/hydrochlorothiazide/amlodipine in severe renal disease (creatinine clearance < 30 mL/min). The usual regimens of therapy with telmisartan/hydrochlorothiazide/amlodipine may be followed if the patient's creatinine clearance is >30 mL/min.

**Hepatic Impairment**

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance.

There are no studies of telmisartan/hydrochlorothiazide/amlodipine in patients with hepatic impairment. Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is prolonged to 56 hrs. in patients with impaired hepatic function. Caution should be exercised when administering amlodipine to patients with severe hepatic impairment.

In patients with impaired hepatic function or progressive liver disease, minor alterations of fluid and electrolyte balance, such as those resulting from diuretic use, may precipitate hepatic coma. Therefore, avoid the use of telmisartan/hydrochlorothiazide/amlodipine in patients with severe hepatic impairment.

When administering telmisartan/hydrochlorothiazide/amlodipine to patients with mild-to-moderate hepatic impairment.

**Pregnancy**

*Pregnancy Category D*

Use of drugs that act on the RAS 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, telmisartan and amlodipine should be discontinued as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with ARBs, similar risks may exist for this class of drugs. Unless continued
ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with ARBs should be stopped immediately, and if appropriate, alternative therapy should be started.
Should exposure to ARB have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ARBs should be closely observed for hypotension. There is limited experience with hydrochlorothiazides during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foeto and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational edema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used. If oligohydramnios is observed, telmisartan/hydrochlorothiazide/amlodipine should be discontinued unless they are 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 telmisartan/hydrochlorothiazide/amlodipine for hypotension, oliguria, and hyperkalemia.

### Lactation

It is not known whether amlodipine and telmisartan are excreted in human milk, but are excreted in rat milk. Thiazides are excreted in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue telmisartan/hydrochlorothiazide/amlodipine, taking into account the importance of the drug to the mother.

### Pediatric Use

*Neonates with a History of In-Utero Exposure to Telmisartan, Amlodipine and Hydrochlorothiazide Combination*

If oliguria or hypotension occurs, support towards BP and renal perfusion should be directed. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Safety and effectiveness in paediatric patients have not been established.

### Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Since patients aged 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. Patients ≥ 75 years of age should start amlodipine at 2.5 mg, therefore initial therapy with telmisartan /hydrochlorothiazide/amlodipine is not recommended in patients ≥ 75 years old.

### Undesirable Effects

#### Clinical Trials Experience

*Telmisartan*

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have only
In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20 to 160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo. Adverse events occurring at an incidence of ≥1% in patients treated with telmisartan and at a greater rate than patients treated with placebo irrespective of their causal association are as listed in the table 1 below:

**Table 1: The incidence of ≥1% of adverse events in patients treated with telmisartan and placebo**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Telmisartan (n = 1455) %</th>
<th>Placebo (n = 380) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

In addition to the adverse events in the table, the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with telmisartan and 6.1% of 380 placebo patients in placebo-controlled clinical trials. The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients. The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebotreated patients (1.6%).

In addition to those listed above, adverse events that occurred in > 0.3% of 3500 patients treated with telmisartan Monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to telmisartan:

**Autonomic Nervous System:** impotence, increased sweating, flushing
**Body as a Whole:** allergy, fever, leg pain, malaise, chest pain
**Cardiovascular:** palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal electrocardiogram (ECG), hypertension, peripheral edema, arrythmias
**Central nervous system (CNS):** insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia, sleep disorders
**Gastrointestinal:** flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders, dyspepsia, abdominal pain, diarrhea
**Hepato-biliary:** elevations of liver enzymes or serum bilirubin
**Metabolic:** gout, hypercholesterolemia, diabetes mellitus, hyperuricemia, blood creatinine increased, blood creatinine phosphokinase (CPK) increased, hypokalemia, hyponatremia
**Musculoskeletal:** arthritis, arthralgia, leg cramps, myalgia, back pain
**Psychiatric:** anxiety, depression, nervousness
Resistance Mechanism: infection, fungal infection, abscess, otitis media
Respiratory: asthma, rhinitis, dyspnea, epistaxis, Respiratory distress (including pneumonitis and pulmonary edema), bronchitis, pharyngitis, sinusitis
Skin: dermatitis, eczema, pruritus, angioedema (also with fatal outcome), erythema, hyperhidrosis, urticarial, exacerbation or activation of systemic lupus erythematosus
Urinary: micturition frequency, cystitis
Vascular: cerebrovascular disorder, hypotension, orthostatic hypotension
Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.
During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings
In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy because of anemia.
Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy because of increases in creatinine and blood urea nitrogen.
Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy because of abnormal hepatic function.

Amlodipine
Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (n=1730) at doses up to 10 mg to placebo (n=1250), discontinuation of amlodipine 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 (Table 2).

Table 2: The incidence (%) of side effects that occurred in a dose related manner is as follows:

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Amlodipine 2.5 mg (n = 275) %</th>
<th>Amlodipine 5 mg (n = 296) %</th>
<th>Amlodipine 10 mg (n = 268) %</th>
<th>Placebo (n = 520) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>1.8</td>
<td>3.0</td>
<td>10.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.1</td>
<td>3.4</td>
<td>3.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Flushing</td>
<td>0.7</td>
<td>1.4</td>
<td>2.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0.7</td>
<td>1.4</td>
<td>4.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Other adverse experiences that were not clearly dose related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following Table 3:
Table 3: Other adverse events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Amlodipine (n = 1730) (%)</th>
<th>Placebo (n = 1250) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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, postural dizziness, postural hypotension, vasculitis, myocardial infarction
- Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo, extrapyramidal syndrome
- Gastrointestinal: anorexia, constipation, dyspepsia**, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia, change in bowel habit
- General: allergic reaction, asthenia**, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease, gynaecomastia
- Psychiatric: sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood change
- Respiratory System: dyspnea**, epistaxis, rhinitis
- Skin and Appendages: angioedema, erythema multiforme, pruritus**, rash**, rash erythematous, rash maculopapular, alopecia, purpura, skin discoloration, hyperhidrosis, urticarial, Stevens-Johnson syndrome, photosensitivity
- Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus
- Urinary System: micturition frequency, micturition disorder, nocturia, pollakiuria
- Autonomic Nervous System: dry mouth, sweating increased.
- Hemopoietic: leukopenia, purpura, thrombocytopenia.

**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, hypotonia, 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.
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. Amlodipine 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.

**Hydrochlorothiazide**

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

- **Body as a Whole**: weakness
- **Digestive**: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation
- **Hematologic**: aplastic anemia, agranulocytosis, leucopenia, hemolytic anemia, thrombocytopenia
- **Hypersensitivity**: purpura, photosensitivity, urticaria, necrotizing angitiis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions
- **Metabolic**: hyperglycemia, glycosuria, anorexia, electrolyte imbalance, hypercholesterolemia, hypovolemia, decreased appetite
- **Musculoskeletal**: muscle spasm
- **Nervous System/Psychiatric**: restlessness, light-headedness
- **Renal**: interstitial nephritis
- **Skin**: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, lupus-like syndrome, skin vasculitis
- **Special Senses**: transient blurred vision, xanthopsia, acute myopia, acute angle-closure glaucoma.

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of telmisartan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan.

**Telmisartan**

- **Blood and Lymphatic System Disorders**: anaemia, thrombocytopenia, eosinophilia, decreased haemoglobin
- **Cardiac Disorders**: atrial fibrillation, congestive heart failure, myocardial infarction, tachycardia, bradycardia
- **Ear and Labyrinth Disorders**: vertigo
- **General Disorders and Administration Site Conditions**: asthenia, edema
- **Hepato-biliary**: Abnormal hepatic function / liver disorder
- **Immune System Disorders**: anaphylactic reaction, hypersensitivity
- **Infections and Infestations**: urinary tract infection including cystitis, sepsis including fatal outcome, stomach discomfort
- **Investigations**: increased CPK
- **Metabolism and Nutrition Disorders**: hypoglycemia (in diabetic patients), hyperkalemia
- **Musculoskeletal and Connective Tissue Disorders**: tendon pain (including tendonitis, tenosynovitis), rhabdomyolysis, arthrosis
- **Nervous System Disorders**: syncope
- **Renal and Urinary Disorders**: renal failure, renal impairment including acute renal failure
- **Reproductive System and Breast Disorders**: erectile dysfunction
Respiratory, Thoracic and Mediastinal Disorders: upper respiratory tract disorders, cough, interstitial lung disease
Skin and Subcutaneous Tissue Disorders: drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), angioedema (with fatal outcome)
Vascular Disorder: orthostatic hypotension.

Amlodipine
Gynecomastia has been reported infrequently and a causal relationship is uncertain. 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.
Postmarketing reporting has also revealed a possible association between extrapyramidal disorder and amlodipine.
If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

Overdosage

Telmisartan
Limited data are available related to over-dosage in humans. The most likely manifestations 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. Telmisartan is not removed by hemodialysis.

Amlodipine
Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional over-dosage of amlodipine is limited.
Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension.
Overdose with amlodipine may result in excessive peripheral vasodilation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine 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, active cardiac and respiratory monitoring should be instituted. Frequent BP measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Hydrochlorothiazide
The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The oral LD₅₀ of hydrochlorothiazide is greater than 10 g/Kg in both mice and rats.
Shelf-Life
Two years

Storage & Handling Instruction
Store in a cool dry place

Packaging Information
CRESAR PLUS: Aluminium pack of 10 tablets
Last Updated: April 2017
Last Reviewed: April 2017

CRESAR PLUS Tablets

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