AMLOPRES-TL Tablets (Telmisartan + Amlodipine)

Composition

AMLOPRES TL Tablets
Each uncoated tablet contains:
Telmisartan .......... 40 mg
Amlodipine Besylate equivalent to Amlodipine ............... 5 mg

Dosage Form

Tablet

Description

AMLOPRES TL Tablets are a combination of two drugs with antihypertensive properties: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker (ARB), telmisartan.

Pharmacology

Pharmacodynamics

The fixed-dose combination of telmisartan and amlodipine tablets has been shown to be effective in lowering blood pressure.

Both telmisartan and amlodipine lower blood pressure by reducing peripheral resistance but through complementary mechanisms.

Telmisartan
Angiotensin II is formed from angiotensin I in a reaction catalysed 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 AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT₁ receptor than for the AT₂ 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 catalysed 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 blood pressure.

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).

Amlodipine

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

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

**Haemodynamics:** 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 haemodynamic 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, the 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 the glomerular filtration rate (GFR) and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic 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 haemodynamic 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.

**Electrophysiologic 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.

**Pharmacokinetics**

The pharmacokinetics of amlodipine and telmisartan when combined are similar to the pharmacokinetics of amlodipine and telmisartan when administered separately.

After administering a fixed-dose combination of telmisartan and amlodipine tablets with a high-fat meal, the total area under the plasma concentration-time curve (AUC) and $C_{\text{max}}$ for telmisartan decreased by about 24% and 60%, respectively. For amlodipine, AUC and $C_{\text{max}}$ were not altered.

**Telmisartan**

Following oral administration, peak concentrations ($C_{\text{max}}$) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the AUC of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. 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 is nonlinear over the dose range of 20-160 mg, with greater than proportional increases of plasma concentrations ($C_{\text{max}}$ and AUC) with
increasing doses. Telmisartan shows bi-exponential decay kinetics, with a terminal elimination half-life of approximately 24 hours. 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 1.5-2.0 upon repeated once-daily dosing.

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 litres indicating additional tissue binding.

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

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 (CY) P450 isoenzymes are not involved in the metabolism of telmisartan.

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

**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.

Elimination of amlodipine 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 7-8 days of consecutive daily dosing.

The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

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.

**Renal Impairment**

**Telmisartan:** No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by haemofiltration.

**Amlodipine:** The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may, therefore, receive the usual initial dose.

**Hepatic Impairment**

**Telmisartan:** In patients with hepatic impairment, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%.

**Amlodipine:** Patients with hepatic impairment have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%. Therefore, start with a low initial dose of
amlodipine.

**Gender**

Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

**Geriatric Patients**

*Telmisartan:* The pharmacokinetics of telmisartan does not differ between the elderly and those younger than 65 years of age.

*Amlodipine:* Elderly patients have decreased clearance of amlodipine, with a resulting increase in AUC of approximately 40-60%. Therefore, start with a low initial dose of amlodipine.

---

### Indications

**AMLOPRES TL Tablets** are indicated for the treatment of hypertension, alone or with other antihypertensive agents to lower blood pressure.

**AMLOPRES TL Tablets** may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

---

### Dosage And Administration

Dosage should be individualized. The recommended dose is one tablet of **AMLOPRES TL Tablets** once daily. If necessary, the dose may be increased to two tablets of **AMLOPRES TL Tablets** once daily. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. The maximum recommended dose of **AMLOPRES TL Tablets** is two tablets once daily.

**AMLOPRES TL Tablets** may be taken with or without food.

---

### Add-on Therapy for Patients with Hypertension Not Adequately Controlled on Antihypertensive Monotherapy

**AMLOPRES TL Tablets** may be used to provide additional blood pressure-lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with telmisartan (or another ARB) alone.

Patients treated with 10 mg amlodipine who experience any dose-limiting adverse reactions such as oedema, may be switched to **AMLOPRES TL Tablets** once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

---

### Initial Therapy

A patient may be initiated on **AMLOPRES TL Tablets** if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of **AMLOPRES TL Tablets** is 40/5
mg once daily. Patients requiring larger blood pressure reductions may be started on two tablets of AMLOPRES TL Tablets once daily.

Initial therapy with AMLOPRES TL Tablets is not recommended in patients ≥75 years old or with hepatic impairment.

Correct imbalances of intravascular volume- or salt-depletion, before initiating therapy with AMLOPRES TL Tablets.

Replacement Therapy

Patients receiving amlodipine and telmisartan from separate tablets may instead receive AMLOPRES TL Tablets containing the same component doses once daily. When substituting for individual components, increase the dose of AMLOPRES TL Tablets if blood pressure control has not been satisfactory.

Dosing in Specific Populations

**Renal Impairment**: No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment.

**Hepatic Impairment**: In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients with hepatic impairment.

**Patients Aged 75 Years and Older**: In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients aged 75 years and older.

Contraindications

AMLOPRES TL Tablets are contraindicated in patients with a known hypersensitivity to telmisartan or amlodipine or any other component of this product.

Do not co-administer aliskiren with AMLOPRES TL Tablets in patients with diabetes.

Warnings And Precautions

Drug Interactions

**Fixed-dose combination of telmisartan and amlodipine tablets**
The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered.

No drug interaction studies have been conducted with telmisartan+amlodipine combination and other drugs, although studies have been conducted with the individual amlodipine and telmisartan components of AMLOPRES TL Tablets, as described below:

Telmisartan
**Aliskiren**: Do not co-administer aliskiren with telmisartan+amlodipine combination in patients with diabetes. Avoid use of aliskiren with AMLOPRES TL Tablets in patients with renal impairment (Glomerular Filtration Rate (GFR)).

**Digoxin**: Digoxin levels should be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization as coadministration of telmisartan and digoxin increases the plasma levels of digoxin.

**Lithium**: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

**Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)**: In patients who are elderly, volume-depleted (including diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically receiving telmisartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

**Ramipril and Ramiprilat**: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state $C_{\text{max}}$ and AUC of ramipril 2.3- and 2.1-fold, respectively, and $C_{\text{max}}$ and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, $C_{\text{max}}$ and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Co-administration of telmisartan and ramipril is not recommended.

**Other drugs**: Coadministration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin 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. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

**Amlodipine**

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics and oral hypoglycemic drugs.

**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 amlodipine to 20 mg daily.

**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 amlodipine is coadministered 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 amlopidine. Patients should be monitored for adequate clinical effect when amlopidine is co-administered with CYP3A4 inducers.

**Other drugs:** The following have no clinically relevant effects on the pharmacokinetics of amlopidine: cimetidine, grapefruit juice, magnesium and aluminum hydroxide antacid, sildenafil. Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, and warfarin.

### Hypotension

In patients with an activated RAS, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with AMLOPRES TL Tablets. This condition should be corrected prior to administration of AMLOPRES TL Tablets, or treatment should start under close medical supervision with a reduced dose. If hypotension does occur, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action of amlopidine, acute hypotension is unlikely.

### Hyperkalaemia

Hyperkalaemia 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.

### Risk of Myocardial Infarction or Increased Angina

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

### Dual Blockade of the Renin Angiotensin Aldosterone System

As a consequence of inhibiting the RAS, changes in renal function (including acute renal failure) have been reported. Dual blockade of the RAS (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

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 compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g. acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is not
Heart Failure

Closely monitor patients with heart failure.

Renal Impairment

As a consequence of inhibiting the RAS, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the RAS system (e.g., patients with severe congestive heart failure), treatment with angiotensin receptor antagonists 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 patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. 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.

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. Initiate telmisartan at low doses and titrate slowly in these patients. Amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5 mg in patients with hepatic impairment. The lowest dose of AMLOPRES TL Tablets is 40/5 mg; therefore, initial therapy with AMLOPRES TL Tablets is not recommended in hepatically impaired patients.

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, AMLOPRES TL Tablets 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. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the RAS from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the RAS for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, AMLOPRES TL Tablets 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 **AMLOPRES TL Tablets** for hypotension, oliguria, and hyperkalemia.

### Lactation

It is not known whether telmisartan or amlodipine is excreted in human milk. In the absence of this information, it is recommended to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

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

If oliguria or hypotension occurs, support towards blood pressure 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

Of the total number of 3,282 hypertensive patients receiving a telmisartan/amlodipine combination in clinical studies, 605 (18%) patients were 65 years of age or older and of these, 88 (3%) patients were aged 75 years and older. No overall differences in effectiveness and safety were observed in these patients compared with younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but the greater sensitivity of some older individuals cannot be ruled out. 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 years and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of **AMLOPRES TL Tablets** is 40/5 mg; therefore, initial therapy with **AMLOPRES TL Tablets** is not recommended in patients ≥75 years of age.

### Undesirable Effects

#### Clinical Trials Experience

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

**Fixed-Dose Combination of Telmisartan and Amlodipine**

The concomitant use of telmisartan and amlodipine has been evaluated for safety in more than 3,700 patients with hypertension; approximately 1,900 of these patients were exposed for at least 6 months and over 160 of these patients were exposed for at least one year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of
In the placebo-controlled factorial design study, the population treated with a telmisartan and amlodipine combination had a mean age of 53 years and included approximately 50% males; 79% were Caucasian, 17% Blacks, and 4% Asians. Patients received doses ranging from 20/2.5 mg to 80/10 mg orally, once daily.

The frequency of adverse reactions was not related to gender, age, or race.

The adverse reactions that occurred in the placebo-controlled factorial design trial in ≥2% of patients treated with a fixed-dose combination of telmisartan and amlodipine and at a higher incidence in patients treated with a fixed-dose combination of telmisartan and amlodipine than placebo-treated patients were peripheral oedema (4.8% vs 0%), dizziness (3.0% vs 2.2%), and back pain (2.2% vs 0%). Oedema (other than peripheral oedema), hypotension, and syncope were reported in <2% of patients treated with the fixed-dose combination of telmisartan and amlodipine tablets.

In the placebo-controlled factorial design trial, discontinuation due to adverse events occurred in 2.2% of all treatment cells of patients in the telmisartan/amlodipine-treated patients and in 4.3% in the placebo-treated group. The most common reasons for discontinuation of therapy with the fixed-dose combination of telmisartan and amlodipine tablets were peripheral oedema, dizziness, and hypotension (each ≤0.5%).

Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine, but not of telmisartan. In the factorial design study, the incidence of peripheral oedema during the 8-week, randomized, double-blind treatment period was highest with amlodipine 10 mg monotherapy. The incidence was notably lower when telmisartan was used in combination with amlodipine 10 mg.

Incidence of Peripheral Oedema during the 8-week Treatment Period with Telmisartan

<table>
<thead>
<tr>
<th>Amlodipine</th>
<th>Telmisartan</th>
<th>Placebo</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0%</td>
<td>0.8%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td>0.7%</td>
<td>1.4%</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>17.8%</td>
<td>6.2%</td>
<td>11.3%</td>
<td></td>
</tr>
</tbody>
</table>

Telmisartan
Telmisartan has been evaluated for safety in more than 3,700 patients, including 1,900 treated for over 6 months and more than 1,300 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1,041 patients treated with various doses of telmisartan (20-160 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 below.

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan (n = 1,455)</th>
<th>Placebo (n = 380)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</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, upper respiratory tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral oedema. 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 the gender, age, or race of patients.

The incidence of cough occurring with telmisartan in six placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in >0.3% of 3,500 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
- **Cardiovascular**: palpitation, dependent oedema, angina pectoris, tachycardia, leg oedema, abnormal ECG
- **CNS**: insomnia, somnolence, migraine, vertigo, paraesthesia, involuntary muscle contractions, hypoesthesia
- **Gastrointestinal**: flatulence, constipation, gastritis, vomiting, dry mouth, haemorrhoids, gastroenteritis, enteritis, gastrooesophageal reflux, toothache, nonspecific gastrointestinal disorders
- **Metabolic**: gout, hypercholesterolaemia, diabetes mellitus
- **Musculoskeletal**: arthritis, arthralgia, leg cramps
- **Psychiatric**: anxiety, depression, nervousness
- **Resistance Mechanism**: infection, fungal infection, abscess, otitis media
- **Respiratory**: asthma, bronchitis, rhinitis, dyspnoea, epistaxis
- **Skin**: dermatitis, rash, eczema, pruritus
- **Urinary**: micturition frequency, cystitis
- **Vascular**: cerebrovascular disorder
- **Special Senses**: abnormal vision, conjunctivitis, tinnitus, earache

During initial clinical studies, a single case of angio-oedema was reported (among a total of 3,781 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.

- **Haemoglobin**: A greater than 2 g/dL decrease in haemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy because of anaemia.

- **Creatinine**: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% of telmisartan patients compared with 0.3% of placebo patients. Therapy was discontinued by 1 telmisartan-treated patient 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 clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine at doses up to 10 mg with placebo, 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 were headache and oedema.

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>Oedema</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 included the following:

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine (n = 1,730) (%)</th>
<th>Placebo (n = 1,250) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7.3</td>
<td>7.8</td>
</tr>
<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 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 ischaemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

**Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paraesthesia, tremor, vertigo.

**Gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhoea, flatulence, pancreatitis, vomiting, gingival hyperplasia, change in bowel habit.

**General:** allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
**Musculoskeletal System:** arthralgia, arthrosis, muscle cramps,** myalgia.

**Psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood change.

**Respiratory System:** dyspnoea,** epistaxis.

**Skin and Appendages:** angio-oedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular.

**Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

**Urinary System:** micturition frequency, micturition disorder, nocturia.

**Autonomic Nervous System:** dry mouth, sweating increased.

**Metabolic and Nutritional:** hyperglycaemia, thirst.

**Haemopoietic:** leucopenia, 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 discolouration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

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

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.

---

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of telmisartan or amlodipine. 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 labelling 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 or amlodipine.

**Telmisartan**

The most frequently spontaneously reported events included the following: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, oedema, face oedema, lower limb oedema,
angioneurotic oedema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalaemia, syncope, dyspepsia, diarrhoea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anaemia, and increased creatinine phosphokinase (CPK), anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (e.g. toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycaemia (in diabetic patients), and angio-oedema (with fatal outcome).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

**Amlodipine**

Gynaecomastia 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.

### Overdosage

#### Telmisartan

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage 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 haemodialysis.

#### Amlodipine

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 an mg/m$^2$ basis) caused a marked peripheral vasodilation and hypotension.

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

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure 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, haemodialysis is not likely to be of benefit.

### Packaging Information
**AMLOPRES TL Tablets**: Strip pack of 10 tablets

*Last updated: March 2014*
*Last reviewed: March 2014*

**AMLOPRES-TL Tablets**

**Source URL**: https://ciplamed.com/content/amlopres-tl-tablets