Natrapharm

Rx

# Telmisartan + Amlodipine

## Vasatraz®

40 mg / 5 mg tablet   80 mg / 5 mg tablet
40 mg / 10 mg tablet   80 mg / 10 mg tablet
Angiotensin II Receptor Blocker (ARB) /
Calcium Channel Blocker

### 1. FORMULATION

Telmisartan/Amlodipine 40mg/5mg Tablet
Each uncoated tablet contains:
Telmisartan .......... 40 mg
Amlodipine (as besilate).......... 5 mg

Telmisartan/Amlodipine 40mg/10mg Tablet
Each uncoated tablet contains:
Telmisartan .......... 40 mg
Amlodipine (as besilate) .......... 10 mg

Telmisartan/Amlodipine 80mg/5mg Tablet
Each uncoated tablet contains:
Telmisartan .......... 80 mg
Amlodipine (as besilate) .......... 5 mg

Telmisartan/Amlodipine 80mg/10mg Tablet
Each uncoated tablet contains:
Telmisartan .......... 80 mg
Amlodipine (as besilate) .......... 10 mg

### 2. PRODUCT DESCRIPTION

TELMISARTAN 40MG AND AMLODIPINE 5MG TABLETS:
Oval shaped biconvex, Bilayer, uncoated tablets with one white to off white color layer and one blue color mottled layer debossed with 'L389'.

TELMISARTAN 40MG AND AMLODIPINE 10MG TABLETS:
Oval shaped biconvex, Bilayer, uncoated tablets with one white to off white color layer and one blue color mottled layer debossed with 'L390'

TELMISARTAN 80MG AND AMLODIPINE 5MG TABLETS
Oval shaped biconvex, Bilayer, uncoated tablets with one white to off white color layer and one blue color mottled layer debossed with 'L391'

TELMISARTAN 80MG AND AMLODIPINE 10MG TABLETS:
Oval shaped biconvex, Bilayer, uncoated tablets with one white to off white color layer and one blue color mottled layer debossed with 'L388'

### 3. DOSAGE FORM

Tablet

### 4. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04.

Telmisartan and amlodipine tablet combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Telmisartan and amlodipine tablet once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Termisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels.

Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse reactions.

In humans, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of substances representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non- dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

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

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

*Use in patients with heart failure*

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Telmisartan/Amlodipine

In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study in 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure ≥ 95 and ≤ 119 mmHg), treatment with each combination dose of Telmisartan and amlodipine tablet resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

Telmisartan and amlodipine tablet showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range of -21.8/-16.5 mmHg (40 mg/5 mg), -22.1/-18.2 mmHg (80 mg/5 mg), -24.7/-20.2 mmHg (40 mg/10 mg) and -26.4/-20.1 mmHg (80 mg/10 mg). The reduction in diastolic blood pressure <90 mmHg was achieved in 71.6 %, 74.8 %, 82.1 %, 85.3 % of patients respectively. Values are adjusted for baseline and country.

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy. In a subset of 1050 patients with moderate to severe hypertension (DBP ≥ 100 mmHg) 32.7 - 51.8 % responded sufficiently to monotherapy of either telmisartan or amlodipine. The observed mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (-22.2/-17.2 mmHg with 40 mg/5 mg; -22.5/-19.1 mmHg with 80 mg/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (-21.0/-17.6 mmHg) and associated with significant lower oedema rates (1.4 % with 40 mg/5 mg; 0.5 % with 80 mg/5 mg; 17.6 % with amlodipine 10 mg).

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic systolic and diastolic blood pressure reductions consistently over the entire 24-hours dosing period.

In a further multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 1097 patients with mild to severe hypertension who were not adequately controlled on amlodipine 5 mg received Telmisartan and amlodipine tablet (40 mg/5 mg or 80mg/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combinations was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures (-13.6/-9.4 mmHg, -15.0/-10.6 mmHg with 40 mg/5 mg, 80 mg/5 mg versus -6.2/-5.7 mmHg, -11.1 /-8.0 mmHg with amlodipine 5 mg and 10 mg and higher diastolic blood pressure control rates compared to the respective monotherapies were achieved (56. 7 %, 63.8 % with 40 mg/5 mg and 80 mg/5 mg versus 42 %, 56.7 % with amlodipine 5 mg and 10 mg). Oedema rates were significantly lower with 40 mg/5 mg and 80 mg/5 mg compared to amlodipine 10 mg (4.4 % versus 24.9 %, respectively).

In another multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 947 patients with mild to severe hypertension who were not adequately controlled on amlodipine 10 mg received Telmisartan and amlodipine tablet (40 mg/10 mg or 80 mg/10 mg) or amlodipine alone (10 mg). After 8 weeks of treatment, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressure (-11.1/-9.2 mmHg, -11.3/-9.3 mmHg with 40 mg/10 mg, 80 mg/10 mg versus -7.4/-6.5 mmHg with amlodipine 10 mg) and higher diastolic blood pressure normalisation rates compared to monotherapy were achieved (63.7 %, 66.5 % with 40 mg/10 mg, 80 mg/10 mg versus 51.1 % with amlodipine 10 mg).

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of Telmisartan and amlodipine tablet was maintained over the trial period. Furthermore it was shown that some patients not adequately controlled with Telmisartan and amlodipine tablet 40 mg/10 mg had additional blood pressure reduction by up-titration to Telmisartan and amlodipine tablet 80 mg/10 mg.

The overall incidence of adverse reactions with Telmisartan and amlodipine tablet in the clinical trial programme was low with only 12.7% of patients on treatment experiencing adverse reactions. The most common adverse reactions were peripheral oedema and dizziness. The adverse reactions reported were in agreement with those anticipated from the safety profiles of the components telmisartan and amlodipine tablet. No new or more severe adverse reactions were observed. The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received Telmisartan and amlodipine tablet as compared to patients who received amlodipine 10 mg. In the factorial design trial the oedema rates were 1.3 % with Telmisartan and amlodipine tablet 40 mg/5 mg and 80 mg/5 mg, 8.8 % with Telmisartan and amlodipine tablet 40mg/5mg and 80mg/5mg, 8.8% with Telmisartan and amlodipine tablet 40 mg/10 mg and 80 mg/10 mg and 18.4 % with Amlodipine 10 mg. In patients not controlled on amlodipine 5 mg the oedema rates were 4.4 % for 40 mg/5 mg and 80 mg/5 mg and 24.9 % for amlodipine 10 mg.

The antihypertensive effect of Telmisartan and amlodipine tablet was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Telmisartan and amlodipine tablet has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25,620 patients with high cardiovascular risk (ONTARGET).

Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Telmisartan and amlodipine tablet in all subsets of the paediatric population in hypertension.

### 5. PHARMACOKINETIC PROPERTIES

Pharmacokinetic of the fixed dose combination

The rate and extent of absorption of Telmisartan and amlodipine tablet are equivalent to the bioavailability of telmisartan and amlodipine tablet when administered as individual tablets.

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. Amlodipine bioavailability is not affected by food ingestion.

Distribution

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500 L.

The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Amlodipine is extensively (approximatively 90%) metabolised by the liver to inactive metabolites.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (Cmax) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cltot) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten percent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Linearity/non-linearity

The small reduction in AUC for telmisartan is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. Cmax and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Amlodipine exhibits linear pharmacokinetics.

Paediatric population (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Gender

Differences in plasma concentrations of telmisartan were observed, with Cmax and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly

The pharmacokinetics of telmisartan do not differ in young and elderly patients.

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

Renal impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hepatic impairment

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life of telmisartan is not changed in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40-60 % in AUC.

### 6. INDICATIONS

Treatment of essential hypertension in adults:

Add on therapy

Telmisartan and amlodipine tablet 40 mg/5 mg is indicated in adults whose blood pressure is not adequately controlled on amlodipine 5 mg alone.

Replacement therapy

Adult patients receiving telmisartan and amlodipine tablet from separate tablets can instead receive tablets of Telmisartan and amlodipine tablet containing the same component doses.

### 7. RECOMMENDED DOSAGE

Posology

The recommended dose of this medicinal product is one tablet per day.

The maximum recommended dose is one tablet 80 mg telmisartan/10 mg amlodipine per day. This medicinal product is indicated for long term treatment.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

*Add on therapy*

Telmisartan and amlodipine tablet 40 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg alone.

Individual dose titration with the components (i.e. amlodipine and telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to Telmisartan and amlodipine tablet 40 mg/5 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

*Replacement therapy*

Patients receiving telmisartan and amlodipine tablet from separate tablets can instead receive tablets of Telmisartan and amlodipine tablet containing the same component doses in one tablet once daily.

*Elderly (>65 years)*

No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.

*Renal impairment*

Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using telmisartan/amlodipine in such patients as amlodipine and telmisartan are not dialysable.

No posology adjustment is required for patients with mild to moderate renal impairment.

*Hepatic impairment*

Telmisartan and amlodipine tablet is contraindicated in patients with severe hepatic impairment.

In patients with mild to moderate hepatic impairment telmisartan/amlodipine should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily.

*Paediatric population*

The safety and efficacy of telmisartan/amlodipine in children aged below 18 years have not been established. No data are available.

Method of administration

Oral use.

Telmisartan and amlodipine tablet can be taken with or without food. It is recommended to take Telmisartan and amlodipine tablet with some liquid.

### 8. METHOD OF ADMINISTRATION

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects. Telmisartan and amlodipine tablet can be taken with or without food. It is recommended to take Telmisartan and amlodipine tablet with some liquid. Telmisartan and amlodipine tablet tablet is for oral use only.

### 9. CONTRAINDICATIONS

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients.
- 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)
- Haemodynamically unstable heart failure after acute myocardial infarction

The concomitant use of telmisartan/amlodipine with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2).

### 10. WARNING AND PRECAUTIONS

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment

Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Furthermore as with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dose recommendations have not been established. Telmlsartan/amlodipine should therefore be used with caution in these patients.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system (RAAS).

Renal impairment and kidney transplantation

When telmisartan/amlodipine is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of telmisartan/amlodipine in patients with a recent kidney transplant. Telmisartan and amlodipine tablet are not dialysable.

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of telmisartan. If hypotension occurs with telmisartan/amlodipine, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions with simulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction

There are no data to support the use of telmisartan/amlodipine in unstable angina pectoris and during or within one month of a myocardial infarction.

Heart failure

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

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia. Hyperkalaemia may be fatal in the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated. The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years)
- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.
- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extensive trauma).

Serum potassium should be monitored closely in these patients.

Other

As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiomyopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.

### 11. INTERACTIONS WITH OTHER MEDICAMENTS

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions common to the combination

No drug interaction studies have been performed.

To be taken into account with concomitant use

*Other antihypertensive medicinal products*

The blood pressure lowering effect of telmisartan/amlodipine can be increased by concomitant use of other antihypertensive medicinal products.

*Medicinal products with blood pressure lowering potential*

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including this medicinal product, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

*Corticosteroids (systemic route)*

Reduction of the antihypertensive effect.

Interactions linked to telmisartan

*Concomitant use not recommended*

*Potassium sparing diuretics or potassium supplements*

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

*Lithium*

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

*Other antihypertensive agents acting on the renin-angiotensin-aldosterone system (RAAS)*

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers 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 RAAS-acting agent.

*Concomitant use requiring caution*

*Non-steroidal anti-inflammatory medicinal products*

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and medicinal products that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

*Ramipril*

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the $AUC_{0-24}$ and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.

*Concomitant use to be taken into account*

*Digoxin*

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49 %) and in trough concentration (20 %) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

Interactions inked to amlodipine

*Concomitant use requiring caution*

*CYP3A4 inhibitors*

With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively, the plasma concentration of amlodipine increased by 22 % and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

*CYP3A4 inducers*

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

*Grapefruit and grapefruit juice*

Concomitant administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine. The concomitant use of amlodipine and grapefruit or grapefruit juice is still not recommended in patients as the bioavailability of amlodipine may increase in some and may result in increased hypotensive effects.

*Concomitant use to be taken into account*

*Tacrolimus*

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

*Cyclosporine*

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

*Simvastatin*

Co-administration of multiple doses of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77% compared to simvastatin alone. Therefore, the dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

*Others*

Amlodipine has been safely administered with digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicinal products (aluminium hydroxide, magnesium hydroxide, simeticone), cimetidine, antibiotics and oral hypoglycaemic medicinal products. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

### 12. STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

There are limited data from the use of telmisartan/amlodipine in pregnant women. Animal reproductive toxicity studies with telmisartan/amlodipine have not been performed.

*Telmisartan*

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.

Studies with telmisartan in animals have shown reproductive toxicity.

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 angiotensin II receptor antagonists, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.

*Amlodipine*

Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 - 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

Because no information is available regarding the use of telmisartan during breast-feeding, telmisartan/amlodipine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while breast-feeding a newborn or preterm infant.

Fertility

No data from controlled clinical studies with the fixed dose combination or with the individual components are available. Separate reproductive toxicity studies with the combination of telmisartan and amlodipine tablet have not been conducted. In preclinical studies, no effects of telmisartan on male and female fertility were observed. Similarly, no effects on male and female fertility were reported for amlodipine.

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been observed for calcium channel blockers in preclinical and in vitro studies. No clinical relevance has been established.

### 13. ADVERSE EFFECTS/ UNDESIRABLE EFFECTS

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients).

Adverse reactions previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with Telmisartan and amlodipine tablet as well, even if not observed in clinical trials or during the post-marketing period.

Tabulated list of adverse reactions

The safety and tolerability of Telmisartan and amlodipine tablet has been evaluated in five controlled clinical studies with over 3,500 patients, over 2,500 of whom received telmisartan in combination with amlodipine.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| System Organ Class | Telmisartan and amlodipine tablet | Telmisartan | Amlodipine |
|---|---|---|---|
| ***Infections and infestations*** | | | |
| Uncommon | | upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis | |
| Rare | cystitis | sepsis including fatal outcome[1] | |
| ***Blood and lymphatic system disorders:*** | | | |
| Uncommon | | anaemia | |
| Rare | | thrombocytopenia, eosinophilia | |
| Very rare | | | leukocytopenia, thrombocytopenia |
| ***Immune system disorders:*** | | | |
| Rare | | hypersensitivity, anaphylactic reaction | |
| Very rare | | | hypersensitivity |
| ***Metabolism and nutrition disorders*** | | | |
| Uncommon | | hyperkalaemia | |
| Rare | | hypoglycaemia (in diabetic patients) | |
| Very rare | | | hyperglycaemia |
| ***Psychiatric disorders*** | | | |
| Uncommon | | | mood change |
| Rare | depression, anxiety, insomnia | | confusion |
| ***Nervous system disorders*** | | | |
| Common | dizziness | | |
| Uncommon | somnolence, migraine, headache, paraesthesia | | |
| Rare | syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor | | |
| Very rare | | | extrapyramidal syndrome |
| ***Eye disorders*** | | | |
| Uncommon | | | visual impairment |
| Rare | | visual disturbance | |
| ***Ear and labyrinth disorders*** | | | |
| Uncommon | vertigo | | tinnitus |
| ***Cardiac disorders*** | | | |
| Uncommon | bradycardia, palpitations | | |
| Rare | | tachycardia | |
| Very rare | | | myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation |
| ***Vascular disorders*** | | | |
| Uncommon | hypotension, orthostatic hypotension, flushing | | |
| Very rare | | | vasculitis |
| ***Respiratory, thoracic and mediastinal disorders*** | | | |
| Uncommon | cough | dyspnoea | dyspnoea, rhinitis |
| Very rare | interstitial lung disease[3] | | |
| ***Gastrointestinal disorder*** | | | |
| Uncommon | abdominal pain, diarrhoea, nausea | flatulence | change of bowel habit |
| Rare | vomiting, gingival hypertrophy, dyspepsia, dry mouth | stomach discomfort | |
| Very rare | | | pancreatitis, gastritis |
| ***Hepato-biliary disorders*** | | | |
| Rare | | hepatic function abnormal, liver disorder[2] | |
| Very rare | | | hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis) |
| ***Skin and subcutaneous tissue disorders*** | | | |
| Uncommon | pruritus | hyperhidrosis | alopecia, purpura, skin discolouration, hyperhidrosis |
| Rare | eczema, erythema, rash | angioedema (with fatal outcome), drug eruption, toxic skin eruption, urticaria | |
| Very rare | | | angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity |
| Not known | | | toxic epidermal necrolysis |
| ***Musculoskeletal and connective tissue disorders*** | | | |
| Uncommon | arthralgia, muscle spasms (cramps in legs), myalgia | | |
| Rare | back pain, pain in extremity (leg pain) | tendon pain (tendinitis like symptoms) | |
| ***Renal and urinary disorders*** | | | |
| Uncommon | | renal impairment including acute renal failure | micturition disorder, pollakiuria |
| Rare | nocturia | | |
| ***Reproductive system and breast disorders*** | | | |
| Uncommon | erectile dysfunction | | gynaecomastia |
| ***General disorders and administration site condition*** | | | |
| Common | peripheral oedema | | |
| Uncommon | asthenia, chest pain, fatigue, oedema | | pain |
| Rare | malaise | influenza-like illness | |
| ***Investigations*** | | | |
| Uncommon | hepatic enzymes increased | blood creatinine increased | weight increased, weight decreased |
| Rare | blood uric acid increased | blood creatine phosphokinase increased, haemoglobin decreased | |

1: the event may be a chance finding or related to a mechanism currently not known
2: most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.
3: cases of interstitial lung disease (predominantly interstitial pneumonia and eosinophilic pneumonia) have been reported from post-marketing experience with telmisartan

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

### 14.OVERDOSAGE AND TREATMENT

Symptoms

Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose of both telmisartan and amlodipine tablet.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and amlodipine tablet are not removed by haemodialysis.

### 15. STORAGE CONDITION

Store at temperatures not exceeding 30°C.

**Caution:**

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

**For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph**
**Seek medical attention immediately at the first sign of any adverse drug reaction.**

### 16. PACKAGING AVAILABLE

Alu-alu Blister pack x 10's (Box of 30's)

### 17. Manufactured by:

Alembic Pharmaceuticals Limited
(Formulation Division)
Village Panelav, P.O. Tajpura,
Near Baska, Taluka : Halol
Panchmahal, Gujarat 389350, India

**Imported and Distributed by:**

Natrapharm Inc.
The Patriot Bldg., South Luzon Express Way, Parañaque, Metro Manila

### 18. REGISTRATION NUMBER:

80 mg / 10 mg: DR-XY49478
80 mg/ 5 mg: DR-XY49479
40 mg/ 10 mg: DR-XY49480
40 mg/ 5 mg: DR-XY49481

**DATE OF FIRST AUTHORIZATION:**

August 2025

**DATE OF REVISION:**

September 2025

20045967