Co-Midis®

1. NAME OF THE MEDICINAL PRODUCT

Co-Midis Tablets 80mg/5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besilate). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Telmisartan / amlodipine layered tablets 80/5 mg are white tablets of oval, biconvex shape; engraved with "747" on one side and "SCP" on the other side. The tablets are for oral administration.

4. CLINICAL PARTICULARS

4.1 Indications

Treatment of essential hypertension.

Replacement Therapy
Patients receiving telmisartan and amlodipine from separate tablets may instead receive Co-Midis containing the same component doses.

Add on therapy
Co-Midis is indicated in patients whose blood pressure is not adequately controlled on telmisartan or amlodipine monotherapy.

Initial therapy
Co-Midis may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. The choice of Co-Midis as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

4.2 Dosage and Administration

DOSAGE

Adults
Co-Midis should be taken once daily.

For patients requiring the 40/5mg, 40/10mg and 80mg/10mg strengths, there are other brands available.

Replacement therapy
Patients receiving telmisartan and amlodipine from separate tablets can instead receive Co-Midis containing the same component doses in one tablet once daily, e.g. to enhance convenience or compliance.

Add on therapy
Co-midis may be administered in patients whose blood pressure is not adequately controlled with amlodipine or telmisartan alone.

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

Initial therapy
A patient may be initiated on telmisartan/amlodipine if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of telmisartan/amlodipine is 40/5 mg once daily. Patients requiring larger blood pressure reductions may be started on telmisartan/amlodipine 80/5 mg once daily.

If additional blood pressure lowering is needed after at least 2 weeks of therapy, the dose may be titrated up to a maximum of 80/10 mg once daily.

Co-Midis can be administered with other antihypertensive drugs.

Special populations

Renal impairment
No posology adjustment is required for patients with renal impairment, including those on haemodialysis. Amlodipine and telmisartan are not dialyzable.

Hepatic impairment
In patients with mild to moderate hepatic impairment Co-Midis should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily.

Elderly Patients
No dose adjustment is necessary for elderly patients.

Normal amlodipine dosage regimens are recommended in the elderly, but increase of dosage should take place with care (see sections Special warnings and precautions, and Pharmacokinetics)

Paediatric population
Co-Midis is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Method of Administration

Tablet for Oral administration
Co-Midis may be taken with or without food

4.3 Contraindications
• Hypersensitivity to the active substances, or to any of the excipients.
• Hypersensitivity to dihydropyridine derivatives
• Second and third trimesters of pregnancy
• Lactation
• Biliary obstructive disorders
• Severe hepatic impairment
• Severe hypotension
• 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 Co-Midis with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see section "Special warnings and precautions") the use of the product is contraindicated.

4.4 Special Warnings 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 anti-hypertensive 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. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Co-Midis 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.

Renal impairment and kidney transplant
When Co-Midis 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 Co-Midis in patients with a recent kidney transplant.
Telmisartan and Amlodipine are not dialyzable.

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 Co-Midis.

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 (see Interactions).

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 stimulation 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 Co-Midis in unstable angina pectoris and during or within one month of a myocardial infarction.

Patients with cardiac failure
In an amlodipine long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Therefore, patients with heart failure should be treated with caution.
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Hyperkalaemia
During treatment with medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with telmisartan.

Diabetes mellitus
In diabetic patients with an additional cardiovascular risk, i.e. patients with diabetes mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with Co-Midis.

Elderly patients
The increase of the amlodipine dosage should take place with care in the elderly patients (see sections Dosage and Administration and Pharmacokinetics)

Other
Co-Midis was effective when treating black patients (usually a low-renin population).

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

4.5 Fertility, Pregnancy and Lactation

The effects of Co-Midis during pregnancy and lactation are not known. Effects related to the mono components are described below.

Pregnancy

Telmisartan:
The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.
The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy. Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.
Angiotensin II receptor antagonists exposure 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).

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.
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:

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses.

Lactation:
Co-Midis is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk . 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 of the potential adverse reactions in nursing infants, a decision

should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of this therapy for the mother (see section contraindication).

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 have not been conducted. In preclinical studies, no effects of telmisartan on male and female fertility were observed.
In some patients treated by calcium channel blockers, reversible biochemical changes in the head of spermatozoa have been reported. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

4.6 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or operating machinery.
If patients experience these adverse experiences, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.7 Side effects

Summary of the safety profile
The safety and tolerability of telmisartan/amlodipine has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.
No additional adverse reactions were identified in clinical trials with the combination telmisartan plus amlodipine compared to the adverse reactions of the monocomponents. Peripheral oedema, a recognised dose dependent adverse reaction of the monocomponent amlodipine, was generally observed at a lower incidence in patients who received the telmisartan/amlodipine combination than in those who received amlodipine alone. Adverse reactions previously reported with one of the monocomponents (telmisartan or amlodipine) may be potential adverse reactions with telmisartan/amlodipine as well, even if not observed in clinical trials or during the post-marketing period. Therefore in addition to the reported adverse reactions during the telmisartan/amlodipine development programme all adverse reactions reported in patients who received telmisartan or amlodipine monotherapy, have been listed for telmisartan/amlodipine.

Tabulated summary of adverse reactions
The following adverse reactions derived from the use of the telmisartan/amlodipine combination or the use of the monocomponents (telmisartan or amlodipine) in clinical trials or from post-marketing experience are shown below classified by MedDRA System organ class and MedDRA Preferred terms.

Infections and infestations
Cystitis

Psychiatric disorders
Depression, anxiety, insomnia

Nervous system disorders
Dizziness, somnolence, migraine, headache, paraesthesia, syncope, neuropathy peripheral, hypoaesthesia, dysgeusia, tremor

Ear and labyrinth disorders
Vertigo

Cardiac disorders
Bradycardia, palpitations

Vascular disorders
Hypotension, orthostatic hypotension, flushing

Respiratory, thoracic and mediastinal disorders
Cough

Gastrointestinal disorders
Abdominal pain, diarrhoea, nausea, vomiting, gingival hypertrophy, dyspepsia, dry mouth

Skin and subcutaneous tissue disorders
Pruritus, eczema, erythema, rash

Musculoskeletal and connective tissue disorders
Arthralgia, muscle spasms (cramps in legs), myalgia, back pain, pain in extremity (leg pain)

Renal and urinary disorders
Nocturia

Reproductive system and breast disorders
Erectile dysfunction

General disorders
Oedema Peripheral, asthenia (weakness), chest pain, fatigue, oedema, malaise

Investigations
Hepatic enzyme increased, blood uric acid increased

Telmisartan:

Infections and infestations
Urinary tract infection, upper respiratory tract infection, sepsis including fatal outcome

Blood and lymphatic system disorders
Anaemia, eosinophilia, thrombocytopenia

Immune system disorders
Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders
Hyperkalaemia, hypoglycaemia (in diabetic patients)

Eye disorders
Visual impairment

Cardiac disorders
Tachycardia

Respiratory, thoracic and mediastinal disorders
Dyspnoea

Gastrointestinal disorders
Flatulence, abdominal discomfort

Hepatobiliary disorders
Hepatic function abnormal/ liver disorder*
*Most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions

Skin and subcutaneous tissue disorders
Angioedema (with fatal outcome), hyperhidrosis, urticaria, drug eruption, toxic skin eruption

Musculoskeletal and connective tissue disorders
Tendon pain (tendonitis like symptoms)

Renal and urinary disorders
Renal impairment including renal impairment (including acute kidney injury)(see also Special warnings and precautions)

General disorders
Influenza like illness

Investigations
Blood creatinine increased, haemoglobin decreased, blood creatine phosphokinase (CPK) increased

Amlodipine:

Blood and lymphatic system disorders
Leukopenia, thrombocytopenia

Immune system disorders
Hypersensitivity

Metabolism and nutrition disorders
Hyperglycaemia

Psychiatric disorders
Mood altered, confusional state

Nervous system disorders
Extrapyramidal disorder, Hypertonia

Eye disorders
Visual impairment, Diplopia

Ear and labyrinth disorders
Tinnitus

Cardiac disorders
Myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation

Vascular disorders
Vasculitis

Respiratory, thoracic and mediastinal disorders
Dyspnoea, rhinitis

Gastrointestinal disorders
Change of bowel habit, pancreatitis, gastritis, Constipation

Hepatobiliary disorders
Hepatitis, jaundice, hepatic enzyme increase (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders
Hyperhidrosis, angioedema, urticaria, alopecia, purpura, skin discolouration, erythema multiforme, dermatitis exfoliative, Stevens-Johnson syndrome, photosensitivity reaction, Toxic epidermal necrolysis

Renal and urinary disorders
Micturition disorder, pollakiuria

Reproduductive system and breast disorders
Gynaecomastia

General disorders
Pain, weight increased, weight decreased

Musculoskeletal and connective tissue disorders
Joint Swelling

4.8 Drug Interactions

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

Interactions linked to the combination
No drug interaction studies have been performed with telmisartan/amlodipine combination and other medicinal products.

Other antihypertensive agents
The blood pressure lowering effect of Co-midis can be increased by concomitant use of other antihypertensive medicinal products.

Agents 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 Co-Midis, e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Interactions linked to telmisartan
Telmisartan may increase the hypotensive effect of other antihypertensive agents.

Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide , glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (39% in a single case), monitoring of plasma digoxin levels should be considered.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC0-24 and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors.
Cases have also been reported with angiotensin II receptor antagonists including telmisartan. Therefore, serum lithium level monitoring is advisable during concomitant use.

Treatment with NSAIDs (i.e. ASA at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the Renin-Angiotensin-System like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.
A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

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 (see Contraindications and Warnings/Precautions).

Aliskiren: Do not co-administer aliskiren with Co-Midis in patients with diabetes. Avoid use of aliskiren with Co-Midis in patient with renal impairment (GFR < 60 ml/min).

Interactions linked to amlodipine
Grapefruit and grapefruit juice
Administration of Co-Midis with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering effects.

CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

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).

Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the

coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia

Simvastatin
Co-administration of multiple doses of 10mg of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77% compared to simvastatin alone. Therefore, limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

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.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors

Additional information
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

4.9 Overdose

Symptoms
There is no experience of overdose with Co-Midis. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.
The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia; bradycardia also occured. 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 may occur.

Therapy
Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Telmisartan and amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: angiotensin II antagonists, plain (telmisartan), combinations with dihydropyridine derivatives (amlodipine), ATC Code: C09DB04.

Mode of action

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

Telmisartan:
Telmisartan is an orally effective 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 effects.
In man, 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.

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.

Pharmacodynamics

Telmisartan:
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 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 SBP. In this respect data concerning DBP are inconsistent.
In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.
The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive drugs (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, lisinopril, ramipril and valsartan).
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.
Telmisartan treatment has been shown in clinical trials to be associated with statistically significant reductions in Left Ventricular Mass and Left Ventricular Mass Index in patients with hypertension and Left Ventricular Hypertrophy .
Telmisartan treatment has been shown in clinical trials (including comparators like losartan, ramipril and valsartan) to be associated with statistically significant reductions in proteinuria (including microalbuminuria and macroalbuminuria) in patients with hypertension and diabetic nephropathy .

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.

Amlodipine:
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

Clinical Trials

Telmisartan:

Prevention of cardiovascular morbidity and mortality
ONTARGET (ONgoin Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of cardiovascular high risk patients.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years. The population studied was 73 % male, 74 % Caucasian, 14 % Asian and 43 % were 65 years of age or older. Hypertension was present in nearly 83 % of randomized patients: 69 % of patients had a history of hypertension at randomization and an additional 14 % had actual blood pressure readings above 140/90 mm Hg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76 %), statins (62 %), beta-blockers (57 %), calcium channel blockers (34 %), nitrates (29 %) and diuretics (28 %).

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure.

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Telmisartan had similar efficacy to ramipril in reducing the primary endpoint. The incidence of the primary endpoint was similar in the telmisartan (16.7 %), ramipril (16.5 %) and telmisartan plus ramipril combination (16.3 %) arms. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019). The treatment effect was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint based on age, gender, race, baseline therapies or underlying disease.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo [131]. The hazard ratio of telmisartan vs. ramipril for this endpoint in ONTARGET was 0.99 (97.5 % CI 0.90 - 1.08, p (non-inferiority) = 0.0004).

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

Amlodipine:

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 or 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.

Fixed dose combination (telmisartan/amlodipine):
In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure ≥ 95 and < 110 mmHg) underwent a 3-4 week placebo run-in period in order to wash out all antihypertensive medications before they were randomised to a double-blind active treatment. Treatment with each combination dose of Telmisartan/Amlodipine resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

The telmisartan/amlodipine combinations showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range:

mmHg reduction	telmisartan/amlodipine dose
21.8/-16.5	40/5 mg
22.1/-18.2	80/5 mg
24.7/-20.2	40/10 mg
26.4/-20.1	80/10 mg

The proportions of patients reaching a diastolic blood pressure < 90 mmHg with a telmisartan/amlodipine combination were:

%	telmisartan/amlodipine dose
71.6%	40/5 mg
74.8%	80/5 mg
82.1%	40/10 mg
85.3%	80/10 mg

A subset of 1050 patients in the factorial design study had moderate to severe hypertension (DBP ≥100 mmHg). In these patients who are likely to need more than one antihypertensive agent to achieve blood pressure goal, the observed mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (-22.2/-17.2 mmHg with 40/5 mg; -22.5/-19.1 mmHg with 80/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (-21.0/-17.6 mmHg). Additionally, combination therapy showed notably lower oedema rates (1.4% with 40/5 mg; 0.5% with 80/5 mg; 17.6% with amlodipine 10 mg).

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy.

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, double-blind, active-controlled study, a total of 1097 patients with mild to severe hypertension who were not adequately controlled on amlodipine 5 mg received telmisartan/amlodipine (40/5 mg or 80/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combination was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures:

mmHg reduction	dose

13.6/-9.4	telmisartan/amlodipine 40/5 mg
15.0/-10.6	telmisartan/amlodipine 80/5 mg
6.2/-5.7	amlodipine 5 mg
11.1/-8.0	amlodipine 10 mg

The proportions of patients with normalisation of blood pressure (trough seated diastolic blood pressure <90 mmHg at the end of the trial) were 56.7% with telmisartan/amlodipine 40/5 mg and 63.8% with telmisartan/amlodipine 80/5 mg compared to 42.0% with amlodipine 5 mg and 56.7% with amlodipine 10 mg.

Oedema related events (peripheral oedema, generalised oedema, and oedema) were significantly lower in patients who received telmisartan/amlodipine (40/5 mg or 80/5 mg) as compared to patients who received amlodipine 10 mg (4.4% vs. 24.9%, respectively).

In another multicentre, double-blind, active-controlled study, a total of 947 patients with mild to severe hypertension who were not adequately controlled on amlodipine 10 mg received telmisartan/amlodipine (40/10 mg or 80/10 mg) or amlodipine alone (10 mg). After 8 weeks, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressures:

mmHg reduction	dose
11.1/-9.2	telmisartan/amlodipine 40/10 mg
11.3/ -9.3	telmisartan/amlodipine 80/10 mg
7.4/-6.5	amlodipine10 mg

The proportions of patients with normalisation of blood pressure (trough seated diastolic blood pressure < 90 mmHg at the end of the trial) were 63.7% with telmisartan/amlodipine 40/10 mg and 66.5% with telmisartan/amlodipine 80/10 mg compared to 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/amlodipine was maintained over the trial period.

In patients not adequately controlled on amlodipine 5 mg, telmisartan/amlodipine achieved similar (40/5 mg) or better (80/5mg) blood pressure control compared to amlodipine 10 mg with significantly less oedema.
In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, telmisartan/amlodipine 40/5 mg or 80/5 mg may achieve similar blood pressure control with less oedema.
The antihypertensive effect of telmisartan/amlodipine was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Telmisartan/amlodipine has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

5.2 Pharmacokinetics properties

Pharmacokinetics of the fixed dose combination
The rate and extent of absorption of telmisartan/amlodipine are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Pharmacokinetic of the single components:

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) 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.
The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

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

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

Metabolism:
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, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan. After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, exclusively as unchanged compound. Cumulative urinary excretion is < 2% of dose. Total plasma clearance (CLtot) is high (approximately 900 ml/min compared with hepatic blood flow (about 1500 mL/min).

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

Paediatric population (age below 18 years)
No pharmacokinetic data for telmisartan/amlodipine are available in the paediatric population.

Gender effects:
Gender differences in plasma concentrations of telmisartan were observed, Cmax and AUC being approximately 3-and 2- fold higher, respectively, in females compared to males without relevant influence on efficacy.

Elderly patients
The pharmacokinetics of telmisartan do not differ between younger and elderly patients.
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life.

Renal impairment
Lower plasma concentrations of telmisartan 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.

Patients with 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 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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, Povidone, Meglumine, Mannitol (Mannogem EZ), Anhydrous Citric Acid, Mannitol, Stearic acid, Croscarmellose Sodium, Magnesium Stearate, Purified water

6.2 Incompatibilities
Not applicable.

6.3 Nature and contents of container
10 tablets per blister strip.
Cartons containing 3 blister strips (10's/Alu-Alu blister x3 blister/box).

6.4 Storage conditions
Do not store above 30 °C.
Store in the original package in order to protect from light and moisture.

7. NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER

Novem Healthcare Pte Ltd
23 New Industrial Road #03-08
Solstice Business Center
Singapore 536209

8. NAME AND ADDRESS OF MANUFACTURER

Standard Chem. & Pharm. Co., Ltd.
No. 6-20, Tuku, Tuku Village, Sinying District, Tainan City, Taiwan

Date of revision : October 2022

Store in a safe place out of the reach of children!