1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

CARDIOTAN

(Telmisartan & Amlodipine Tablets 80 / 10 mg)

2. Quality and Quantitative Composition

Qualitative Composition:

Each Uncoated Bi-layered Tablet contains:-

Telmisartan BP……..80 mg

Amlodipine Besilate BP

Eq. to Amlodipine …….10 mg

Excipients…….Q.S.

Colour: Ponceau 4 R

Sr. No.	Ingredients	Standard
Telmisartan Layer (Layer I)		
1	Sodium Hydroxide	BP
2	Microcrystalline cellulose	BP
3	Lactose	BP
4	Croscarmellose Sodium	BP
5	Ponceau 4 R	IH
6	Purified Talc	BP

7	Magnesium Stearate	BP
8	Colloidal Anhydrous Silica	BP
9	Indion Resin	IH
10	Sodium Lauryl Sulfate	BP
11	Kyron T-314	IH
Amlodipine Layer (Layer II)		
1	Maize Starch	BP
2	Colloidal Anhydrous Silica	BP
3	Croscarmellose Sodium	BP
4	Purified Talc	BP
5	Magnesium Stearate	BP
6	Sodium Lauryl Sulfate	BP

Quantitative Composition:

Each Uncoated Bi-layered Tablet contains:-

Telmisartan BP……..80 mg

Amlodipine Besilate BP

Eq. to Amlodipine …….10 mg

Excipients…….Q.S.

Colour: Ponceau 4 R

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Sr. No.	Ingredients	Standard	Quantity / Tablet
Telmisartan Layer (Layer I)			
1	Sodium Hydroxide	BP	0.80 mg
2	Microcrystalline cellulose	BP	105.40 mg
3	Lactose	BP	95.50 mg
4	Croscarmellose Sodium	BP	15.00 mg

5	Ponceau 4 R	IH	1.40 mg
6	Purified Talc	BP	5.50 mg
7	Magnesium Stearate	BP	2.80 mg
8	Colloidal Anhydrous Silica	BP	4.60 mg
9	Indion Resin	IH	5.50 mg
10	Croscarmellose Sodium	BP	20.00 mg
11	Sodium Lauryl Sulfate	BP	6.40 mg
12	Kyron T-314	IH	5.50 mg
Amlodipine Layer (Layer II)			
1	Maize Starch	BP	110.72 mg
2	Colloidal Anhydrous Silica	BP	1.50 mg
3	Croscarmellose Sodium	BP	2.00 mg
4	Maize Starch	BP	4.50 mg
5	Purified Talc	BP	2.00 mg
6	Magnesium Stearate	BP	1.50 mg
7	Colloidal Anhydrous Silica	BP	1.50 mg
8	Sodium Lauryl Sulfate	BP	6.00 mg
9	Croscarmellose Sodium	BP	6.00 mg

3. Pharmaceutical Form

Solid Dosage form (Tablets)

White and Pink coloured Bilayered, round, biconvex tablets, both side plain.

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Add on therapy

Telmisartan & Amlodipine Tablets 80 / 10 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 from separate tablets can instead receive tablets of Telmisartan & Amlodipine Tablets 80 / 10 mg containing the same component doses.

4.2 Posology and method of administration

Posology

The recommended dose of this medicinal productis one tablet per day.

The maximum recommended dose is one tablet 80 mg telmisartan/10mg amlodipine per day. This medicinal productis 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 & Amlodipine Tablets 80 / 10 mg is indicated in adults whose blood pressure is not adequately controlled on amlodipine 5 mg alone.

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

Patients treated with 10mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to Telmisartan & Amlodipine Tablets 80 / 10 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Replacement therapyPatients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Telmisartan & Amlodipine Tablets 80 / 10 mg containing the same component doses in one tablet once daily.

Elderly (> 65years)

No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.Normal amlodipinedosage regimens are recommended in the elderly, but increase of dosageshould take place with care.

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 & Amlodipine Tablets 80 / 10 mg 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 40mg 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 & Amlodipine Tablets 80 / 10 mg can be taken with or without food. It is recommended to take Telmisartan & Amlodipine Tablets 80 / 10 mg with some liquid.

4.3 Contraindication

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients used.
- 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)

4.3 Special Warnings and precautions for use

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.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. Telmisartan/amlodipineshould 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/amlodipineis 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/amlodipinein patients with a recent kidney transplant. Telmisartan and amlodipine 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 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 telmisartan/amlodipinein unstable angina pectoris and during or within onemonth 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.

Diabetic patients treated with insulinor 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-aldosteronesystem, the benefit risk ratioshould be evaluated.

The main risk factors for hyperkalaemia to be considered are:

-Diabetes mellitus, renal impairment, age (>70years)

-Combination with one or more other medicinal products that affect the renin-angiotensin-aldosteronesystem and/orpotassium 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.

Elderly patientsThe increase of the amlodipine dosage should take place with care in the elderly patients.

Other

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

4.4 Interaction with other medicinal products and other forms of interaction

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.

To be taken into account with concomitant use

Other antihypertensive medicinal products

The blood pressure loweringeffect of telmisartan/amlodipinecan 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 useis 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-aldosteronesystem (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 AUC0-24 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 linked to amlodipine

Concomitant use requiring caution

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 varies. Therefore, blood pressure should be monitored and dose regulation considered bothduring 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.

Grapefruit and grapefruit juiceAdministration of Telmisartan & Amlodipine Tablets 80 / 10 mg with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering 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 reductionsshould 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, amlodipinemay increase exposure of mTOR inhibitors.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with simvastatin 80mg 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 20mg daily.

4.5 Pregnancy and lactation

Pregnancy

There are limiteddata 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 haveshown 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

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

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/amlodipineis 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 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.

4.7. Effects on ability to drive and use machines

This medicinal producthas moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8. Undesirable effects

- A light-headed feeling, like you might pass out;
- Shortness of breath (even with mild exertion), swelling, rapid weight gain;

- New or worsened chest pain;
- Pounding heartbeats or fluttering in your chest;
- Tremors, muscle stiffness or twitching; or
- High potassium--nausea, slow or unusual heart rate, weakness, loss of movement.

Common side effects may include:

- Swelling in your hands or feet;
- Fast or pounding heartbeats;
- Dizziness, drowsiness;
- Flushing (warmth, redness, or tingly feeling);
- Back pain; or
- Nausea, diarrhea, stomach pain.

4.9. Overdose 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 ofoverdose of both telmisartan and amlodipine.

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. 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 Pharmacodynamic Properties

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

Telmisartan and Amlodipine combine's 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 once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan

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 AT1receptor. 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 (kininaseII), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse reactions.

In humans, an 80mg 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 48hours.

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4to 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 4hours 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 40and 80mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time torecovery 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. VANEPHRON-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 frequentlyreported 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, oncedaily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24hour 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.

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 ≤119mmHg), treatment with each combination dose of Telmisartan and Amlodipine resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

Telmisartan and Amlodipine showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range of –21.8/–16.5 mmHg (40 mg/5mg), –22.1/–18.2 mmHg (80 mg/5mg), –24.7/–20.2mmHg (40 mg/10mg) and –26.4/–20.1 mmHg (80 mg/10mg). The reduction indiastolic 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≥100mmHg) 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 5mg (–22.2/–17.2mmHg with 40mg/5mg; –22.5/–19.1mmHg with 80mg/5mg) were comparable to or greater than those seen with amlodipine 10mg (–21.0/–17.6 mmHg) and associated with significant lower oedema rates (1.4% with 40mg/5mg; 0.5% with 80mg/5mg; 17.6% with amlodipine 10mg).

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562patients 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 5mg received Telmisartan and Amlodipine (40 mg/5mg or 80mg/5mg) or amlodipine alone (5mg or 10mg).

After 8weeks 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/–10.6mmHg with 40 mg/5mg, 80 mg/5mg versus –6.2/–5.7 mmHg, –11.1/–8.0 mmHg with amlodipine 5mg and 10mg and higher diastolicblood pressure control rates compared to the respective monotherapies were achieved (56.7%, 63.8% with 40mg/5mg and 80mg/5mg versus 42%, 56.7%with amlodipine 5mg and 10mg). Oedema rates were significantly lower with 40 mg/5mg and 80 mg/5mg compared to amlodipine 10mg (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 10mg received Telmisartan and Amlodipine(40 mg/10mg or 80mg/10mg) or amlodipine alone (10mg). 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 40mg/10mg, 80mg/10mg versus –7.4/–6.5 mmHg with amlodipine 10mg) and higher diastolic blood pressure normalisation rates compared to monotherapy were achieved (63.7%, 66.5% with 40 mg/10mg, 80mg/10 mg versus 51.1% with amlodipine 10mg).

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

The overall incidence of adverse reactions with Telmisartan and Amlodipine 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 andamlodipine. 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 Amlodipineas compared to patients who received amlodipine 10mg. In the factorial design trial the oedema rates were 1.3% with Telmisartan and Amlodipine 40 mg/5mg and 80mg/5mg, 8.8% with Telmisartan and Amlodipine 40 mg/10mg and 80mg/10mg and 18.4%with Amlodipine 10mg. In patients not controlled on amlodipine 5mg the oedema rates were 4.4% for 40 mg/5mg and 80 mg/5mg and 24.9% for amlodipine 10mg.

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

Telmisartan and Amlodipine have not been studied in any patient populationother 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 Amlodipinein all subsets of the paediatric population in hypertension.

5.2 Pharmacokinetic Properties

Pharmacokinetic of the fixed dose combination The rate and extent of absorption of Telmisartan and Amlodipine are equivalent to the bioavailability of telmisartan and amlodipine 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 (AUC0-∞) of telmisartan varies from approximately 6%(40 mg dose) to approximately 19% (160mg 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 64and 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 500.1.

The volume of distribution of amlodipine is approximately 21l/kg. In vitrostudies 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 shownfor 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 >20hours. 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 1,000ml/min) compared with hepatic blood flow (about 1,500ml/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 per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Linearity/non-linearityThe 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.

ElderlyThe 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.

5.3 Preclinical safety data

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10mg/kg of telmisartan and amlodipine were tested.

Preclinical data available for the components of this fixed dose combination are reported below.

Telmisartan

In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral saline supplementation. In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.

No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offspring such as lower body weight and delayed eye opening was observed.

There was no evidence of mutagenicity and relevant clastogenic activity in in vitrostudies and no evidence of carcinogenicity in rats and mice.

Amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64days and females for 14days prior to mating) at doses of up to 10mg amlodipine/kg/day (about 8 times* the maximum recommended human dose of 10mg/day on an mg/m2basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinicaldose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg.

6. 0 Pharmaceutical Particulars

6.1 List of excipients

Sr. No.	Ingredients	Standard
Telmisartan Layer (Layer I)		

1	Sodium Hydroxide	BP
2	Microcrystalline cellulose	BP
3	Lactose	BP
4	Croscarmellose Sodium	BP
5	Ponceau 4 R	IH
6	Purified Talc	BP
7	Magnesium Stearate	BP
8	Colloidal Anhydrous Silica	BP
9	Indion Resin	IH
10	Sodium Lauryl Sulfate	BP
11	Kyron T-314	IH
Amlodipine Layer (Layer II)		
1	Maize Starch	BP
2	Colloidal Anhydrous Silica	BP
3	Croscarmellose Sodium	BP
4	Purified Talc	BP
5	Magnesium Stearate	BP
6	Sodium Lauryl Sulfate	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C protected from light.

6.5 Nature and contents of container

Alu/Alu Blister pack of 10 x 10 Tablets.

6.6 Special precautions for disposal

Telmisartan should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder/ Applicant

SWISS PHARMA NIG. LTD

5 Dopemu Road Agege Lagos, Nigeria

8. Marketing Authorization Numbers

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9. Date of first authorization/renewal of the authorization

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10. Date of revision of the text
