1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

CARDIOTAN HCT

(Telmisartan, Amlodipine and Hydrochlorothiazide Tablets 40 / 5 / 12.5 mg)

2. Quality and Quantitative Composition

Qualitative Composition:

Each Uncoated Bi-layered Tablet contains:-

Telmisartan BP……..40 mg

Amlodipine Besilate BP

Eq. to Amlodipine …….5 mg

Hydrochlorothiazide BP….12.5 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 + HCTZ 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……..40 mg

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Eq. to Amlodipine …….5 mg

Hydrochlorothiazide BP….12.5 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	0.40 mg
2	Microcrystalline cellulose	BP	81.80 mg

3	Lactose	BP	80.00 mg
4	Croscarmellose Sodium	BP	10.00 mg
5	Ponceau 4 R	IH	1.00 mg
6	Purified Talc	BP	4.00 mg
7	Magnesium Stearate	BP	2.00 mg
8	Colloidal Anhydrous Silica	BP	4.00 mg
9	Indion Resin	IH	4.00 mg
10	Croscarmellose Sodium	BP	4.00 mg
11	Sodium Lauryl Sulfate	BP	4.00 mg
12	Kyron T-314	IH	4.00 mg
Amlodipine + HCTZ Layer (Layer II)			
1	Maize Starch	BP	69.11 mg
2	Colloidal Anhydrous Silica	BP	1.50 mg
3	Croscarmellose Sodium	BP	2.00 mg
4	Maize Starch	BP	5.00 mg
5	Purified Talc	BP	1.50 mg
6	Magnesium Stearate	BP	1.50 mg
7	Colloidal Anhydrous Silica	BP	1.50 mg
8	Sodium Lauryl Sulfate	BP	9.00 mg
9	Croscarmellose Sodium	BP	9.00 mg

3. Pharmaceutical Form

Solid Dosage form (Tablets)

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

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

This fixed dose combination is not indicated for initial therapy

4.2 Posology and method of administration

Posology

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

Cardiotan HCT may be substituted for its individually titrated components for patients on telmisartan, amlodipine, and hydrochlorothiazide. Cardiotan HCT may be used as add-on/switch therapy to provide additional blood pressure lowering for patients not adequately controlled on agents from two of the following antihypertensive classes: angiotensin receptor blockers, calcium channel blockers, and diuretics at their maximally tolerated, labeled, or usual dose.

Special Populations:

Pediatric Use

Safety and effectiveness in paediatric patients has not been established

Geriatric Use

Telmisartan and Hydrochlorothiazide

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy

Amlodipine

Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required.

Patients with Renal Impairment

Safety and effectiveness in patients with severe renal impairment (CrCl ≤30 mL/min) have not been established. Not recommended in patients with severe renal impairment. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

Patients with Hepatic Impairment

Telmisartan

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

Hydrochlorothiazide

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5mg. Since the dose of Cardiotan HCT is 40/5/12.5mg, Cardiotan HCT is not recommended in hepatically impaired patients.

4.3 Contraindication

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients used.
- In patients with anuri
- Do not co-administer with aliskiren in patients with diabetes
- Severe hepatic impairment.

- Severe renal impairment (creatinine clearance <30 ml/min).
- Refractory hypokalaemia, hypercalcaemia.

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

Telmisartan and Hydrochlorothiazide

Agents Increasing Serum Potassium

Co-administration of telmisartan with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients.

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 juice Administration of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets 40 / 5 / 12.5 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

Cardiotan HCT can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death.

Use of drugs that act on the RAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death.

In patients taking Cardiotan HCT during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue Cardiotan HCT, unless it is considered lifesaving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of in utero exposure to Cardiotan HCT for hypotension, oliguria, andhyperkalemia. If oliguria or hypotension occurs, support blood pressure and renal perfusion.

Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Lactation

There is no information regarding the presence of Cardiotan HCT or telmisartan in human milk, the effects on the breastfed infant or the effects on milk production.

Telmisartan is present in the milk of lactating rats. Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with Cardiotan HCT.

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

Telmisartan and hydrochlorothiazide

The following adverse reactions are discussed elsewhere in labeling:

• Hypotension

• Renal Impairment

• Electrolytes and Metabolic Disorders

Common adverse effects ≥2%: Fatigue, influenza like symptoms, dizziness, nausea, diarrhea, sinusitis and upper respiratory tract infection.

The most common adverse reaction to amlodipine is oedema which occurred in dose related manner. Other adverse experiences not dose related but reported with an incidence >1.0% are fatigue, nausea, abdominal pain and somnolence.

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.
- 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.

4.9. Overdose and treatment

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If

digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

Amlodipine

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

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

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

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.

Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 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 events.

An 80 mg dose of telmisartan administered to healthy volunteers 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.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

Clinical efficacy and safety

Treatment of essential hypertension

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4-8 weeks after the start of treatment and is sustained during long-term therapy. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by measurements made at the point of maximum effect and immediately prior to the next dose (through to peak ratios consistently above 80% after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies).

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 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.

Cardiovascular prevention

ONTARGET (ONgoing 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, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.

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.

Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among telmisartan and ramipril treated patients, respectively.

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

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p=0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

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. For more detailed information see above under the heading “Cardiovascular prevention”.

VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

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

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

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

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.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all cause mortality were numerically higher with the combination. 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.

In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00-2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14-3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

The effects of fixed dose combination of telmisartan/HCT on mortality and cardiovascular morbidity are currently unknown.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg)

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with telmisartan hydrochlorothiazide in 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.

Telmisartan /Hydrochlorothiazide

Concomitant administration of hydrochlorothiazide and telmisartan does not appear to affect the pharmacokinetics of either substance in healthy subjects.

<u>Absorption</u>

Telmisartan: Following oral administration, peak concentrations of telmisartan are reached in 0.5-1.5 h after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42% and 58%, respectively. Food slightly reduces the bioavailability of telmisartan with a reduction in the area under the plasma concentration time curve (AUC) of about 6% with the 40 mg tablet and about 19% after a 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. Telmisartan does not accumulate significantly in plasma on repeated administration.

Hydrochlorothiazide: Following oral administration of telmisartan/hydrochlorothiazide, peak concentrations of hydrochlorothiazide are reached in approximately 1.0-3.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60%.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%) mainly albumin and alpha l-acid glycoprotein. The apparent volume of distribution for telmisartan is approximately 500 litres indicating additional tissue binding.

Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.83-1.14 l/kg.

Biotransformation

Telmisartan is metabolised by conjugation to form a pharmacologically inactive acylglucuronide. The glucuronide of the parent compound is the only metabolite that has been identified in humans. After a single dose of ^{14}C-labelled telmisartan the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Hydrochlorothiazide is not metabolised in man.

Elimination

Telmisartan: Following either intravenous or oral administration of ^{14}C-labelled telmisartan most of the administered dose (>97%) was eliminated in faeces via biliary excretion. Only minute amounts were found in urine. Total plasma clearance of telmisartan after oral administration is >1500 ml/min. Terminal elimination half-life was >20 hours.

Hydrochlorothiazide is excreted almost entirely as unchanged substance in urine. About 60% of the oral dose is eliminated within 48 hours. Renal clearance is about 250-300 ml/min. The terminal elimination half-life of hydrochlorothiazide is 10-15 hours.

Linearity/non-linearity

Telmisartan: The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses.

Hydrochlorothiazide exhibits linear pharmacokinetics.

Elderly

Pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

Gender

Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dose adjustment is necessary. There was a trend towards higher plasma concentrations of hydrochlorothiazide in female than in male subjects. This is not considered to be of clinical relevance.

Renal impairment

Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild to moderate renal impairment (creatinine clearance of 30-60 ml/min, mean about 50 ml/min) no dose adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by haemodialysis. In patients with impaired renal function the rate of hydrochlorothiazide elimination is reduced. In a typical study in patients with a mean creatinine

clearance of 90 ml/min the elimination half-life of hydrochlorothiazide was increased. In functionally anephric patients the elimination half-life is about 34 hours.

Hepatic impairment

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%. The elimination half-life is not changed in patients with hepatic impairment.

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.

Telmisartan /Hydrochlorothiazide

In preclinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs, doses producing exposure comparable to that in the clinical therapeutic range caused no additional findings not already observed with administration of either substance alone. The toxicological findings observed appear to have no relevance to human therapeutic use.

Toxicological findings also well known from preclinical studies with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists were: a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit), changes of renal haemodynamics (increased blood urea nitrogen and creatinine), increased plasma renin activity, hypertrophy/hyperplasia of the juxtaglomerular cells and gastric mucosal injury. Gastric lesions could be prevented/ameliorated by oral sodium chloride solution supplementation and group housing of animals. In dogs renal tubular dilation and atrophy were observed. These findings are considered to be due to the pharmacological activity of telmisartan.

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

Telmisartan showed no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice. Studies with hydrochlorothiazide have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models. However, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

For the foetotoxic potential of the telmisartan/hydrochlorothiazide combination

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 + HCTZ 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
