Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Cilnidipine 5 mg and telmisartan 40 mg tablet
Cilnidipine 10 mg and telmisartan 80 mg tablet

2. Qualitative and quantitative composition

CILVAS-TEL 5mg/40mg:
Each film coated tablet contains Cilnidipine 5 mg and telmisartan 40 mg tablet.
This product contains ethanol 0.040mg, mannitol 20mg, and lactose 20mg.
CILVAS-TEL 10mg/80mg:
Each film coated tablet contains Cilnidipine 10 mg and telmisartan 80 mg tablet.
This product contains ethanol 0.080mg, mannitol 40mg, and lactose 40mg.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film Coated Tablets
CILVAS-TEL 5mg/40mg: Yellow coloured film coated tablet
CILVAS-TEL 10mg/80mg: Red coloured film coated tablet

4. Clinical particulars

4.1 Therapeutic indications

Adults:
Treatment of essential hypertension in adults.
CILVAS-TEL 5/40 & CILVAS-TEL 10/80 is indicated in adults whose Blood Pressure (BP) is not adequately controlled on Cilnidipine or Telmisartan monotherapy.

4.2 Posology and method of administration

Adults: The recommended dose is once daily.
CILVAS-TEL 5/40 may be administered in patients whose Blood Pressure (BP) is not adequately controlled with Cilnidipine 5 mg or Telmisartan 40 mg alone.
CILVAS-TEL 10/80 may be administered in patients whose Blood Pressure (BP) is not adequately controlled with Cilnidipine 10 mg or Telmisartan 80 mg alone.

Children and adolescents:
This medication hasn't been studied in children and shouldn't be used in children under the age of 18 years.

4.3 Contraindications

- Hypersensitivity to the active ingredient or any excipient of CILVAS-TEL 5/40 and CILVAS-TEL 10/80 tablets.

- Cardiogenic shock, Severe aortic Stenosis.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• Second and third trimester of pregnancy (see sections 4.4 and 4.6).
• Biliary obstructive disorders.
• Severe hepatic impairment.
• The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.5 and 5.1).
Left ventricular outflow tract obstruction and untreated congestive cardiac failure.
• Unstable angina pectoris or recent (within 1 month) myocardial infarction, Severe hepatic impairment and Severe renal impairment (GFR < 30 ml/min), including patients undergoing dialysis
•Co-administration with Strong inhibitors of CYP3A4, Ciclosporin, grapefruit or grapefruit juice are also contra-indicated.

4.4 Special warnings and precautions for use

Telmisartan

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 not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment, since Telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for Telmisartan. Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.

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 reninangiotensin-aldosterone system.

Renal impairment and kidney transplantation: When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended.

There is no experience regarding the administration of Telmisartan in patients with recent kidney transplantation.

Intravascular hypovolaemia: Symptomatic hypotension, especially after the first dose of Telmisartan, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, or vomiting. Such conditions should be corrected before the administration of Telmisartan. Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.

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 such as Telmisartan 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.
Diabetic patients treated with insulin or antidiabetics: In these patients hypoglycaemia may occur under Telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.
Hyperkalaemia: The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.
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, hyperkalaemia may be fatal. Before considering the concomitant use of medicinal products that affect the reninangiotensin-aldosterone system, the benefit risk ratio should be evaluated. The main risk factors for hyperkalaemia to be considered are:
- Diabetes mellitus, renal impairment, age (>70 years)
- Combination with one or more other medicinal products that affect the reninangiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium- sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.

- Intercurrent events, in particular dehydratation, 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, extend trauma).
Close monitoring of serum potassium in at risk patients is recommended.
Ethnic differences: As observed for angiotensin converting enzyme inhibitors, Telmisartan and the other angiotensin II receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

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

Cilnidipine
• Cilnidipine should be used with caution in patients with hypotension (low blood pressure), heart failure and poor cardiac reserve.
• Cilnidipine should be discontinued in patients who feel chest pain following the administration of the drug.
• Sudden withdrawal of the drug to be avoided as this may exacerbate angina. Therefore, if the discontinuation of Cilnidipine Tablets is necessary, the dosage should be gradually decreased under close observation. If Cilnidipine Tablets is withdrawn from a daily dose of 5 mg, appropriate measures, such as replacement with other antihypertensive agents, should be taken.
Direct the patient not to discontinue this drug without physician's instructions.
• Cilnidipine is not recommended for use in pregnancy and during breastfeeding,
• Cilnidipine should be used with caution if you have liver problems i.e. an impaired liver can lead to the accumulation of this medicine and cause serious side effects
• Cilnidipine should be used with caution in severe kidney problems
•Cilnidipine 10mg tablet is not recommended for use in children below 18 years
•Antiepileptic drugs such as phenytoin and carbamazepine and other drugs include rifampin, quinidine and aldesleukin should also be used with caution along with Cilnidipine.

4.5 Interaction with other medicinal products and other forms of interaction

Telmisartan
Digoxin: When co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.
Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with

angiotensin II receptor antagonists including Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.
Ramipril and Ramiprilat: Coadministration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3- and 2.1- fold, respectively, and Cmax and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, Cmax and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Concomitant use of CILVAS TEL and ramipril is not recommended.
Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit SUMMARY OF PRODUCT CHARACTERISTICS (SPC) cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Cilnidipine
Cilnidipine can interact with aldesleukin, quinidine, phenytoin, rifampicin, erythromycin, other antihypertensive drugs and anti-psychotic drugs.
Cilnidipine Tablets is chiefly metabolized by the drug-metabolizing enzyme CYP3A4 and in part by CYP2C19. Cilnidipine interacts with the following drugs:
- Antipsychotic drugs combined with cilnidipine may result in low blood pressure
- Anti-diabetes medications along with this drug may result in changes in glucose levels, therefore monitoring of glucose levels may be required
- Antiepileptic drugs such as phenytoin and carbamazepine and other drugs include rifampin, Primaquine, Cimetidine, erythromycin, quinidine and aldesleukin
- Consumption of grapefruit juice while taking Cilnidipine can increase the absorption of this medicine in your body
- Caution is advised when consuming alcohol with Cilnidipine
- The blood levels of Amlodipine and Cilnidipine are possibly raised by concurrent use.

Precautions for Coadministration (Cilnidipine Tablets and the following drugs should be administered with care.)

Names of Drugs	**Signs, Symptoms and Treatment**	**Mechanism and Risk Factors**
Agents with hypotensive effect	There is a possibility that blood pressure is excessively decreased.	Drug action is considered to be enhanced additively or synergistically.
Digoxin	It has been reported that some other calcium antagonists (e.g., nifedipine) increased the plasma concentration of digoxin. If any toxic signs/symptoms attributable to digoxin (e.g., nausea, vomiting, headache, abnormal vision, arrhythmia) are observed, appropriate measures should be instituted such as digoxin dose adjustment or	The mechanism is not completely clarified yet, but is thought to lie in decreased renal and extrarenal clearances.

	discontinuation of Cilnidipine Tablets, depending on the patient's condition	
Cimetidine	It has been reported that effects of some other calcium antagonists (e.g., nifedipine) were enhanced.	It is thought that cimetidine decreases hepatic blood flow with the consequent suppression of the enzymatic metabolism of calcium antagonists in liver microsomes, and at

		the same time cimetidine lowers gastric acid output and thus increases absorption of calcium antagonists.
Rifampicin	It has been reported that effects of other calcium antagonists (e.g., nifedipine) were reduced.	It is generally thought that hepatic drug-metabolizing enzyme (cytochrome P-450) induced by rifampicin facilitates metabolism of calcium antagonists and thus increases the clearance of these agents.
Antifungal azoles: Itraconazole, miconazole	The blood concentration of Cilnidipine Tablets may be elevated.	Antimycotic azoles are thought to inhibit CYP3A4, a drug metabolizing enzyme for Cilnidipine Tablets.
Grapefruit juice	It has been demonstrated that the plasma concentration of Cilnidipine Tablets is elevated.	Details of the underlying mechanism remain to be elucidated, but some constituents in grapefruit juice may inhibit CYP3A4, a drug metabolizing enzyme for Cilnidipine Tablets.

4.6 Pregnancy and Lactation

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.

Breast-feeding & Fertility

Cilnidipine Tablets should not be administered to women having possibilities of being pregnant. [It has been reported that Cilnidipine Tablets prolongs the gestation period and delivery time in animal experiments (in rats).

Cilnidipine is not recommended for use while breastfeeding. If you are breastfeeding, consult your doctor before taking this medicine.

Pregnant and lactating women should avoid using this tablet, it may lead fetal toxicity.

4.7 Effects on ability to drive and use machines

Driving and working near heavy machinery is prohibited because of dizziness.

4.8 Undesirable effects

Telmisartan

Serious adverse reactions include anaphylactic reaction and angioedema which may occur rarely (≥1/10,000 to <1/1,000), and acute renal failure.

The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4% vs 43.9%) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term studies including 21,642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

Tabulated summary of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention:

very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (< 1/10,000)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

:

System Organ Class	**Common (≥ 1/100 to**	**Uncommon (≥ 1/1,000 to <1/100)**	**Rare (≥ 1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**

	<1/10)			
Infections and infestations	-	Upper respiratory tract infection, urinary tract infection	Sepsis (including fatal outcome)	-
Blood and lymphatic system disorders	-	Anaemia	Eosinophilia, thrombocytopenia	-
Immune system disorders	-	-	Anaphylactic reaction, hypersensitivity	-
Metabolism and nutrition disorders	-	Hyperkalaemia	Hypoglycaemia (in diabetic patients)	-
Psychiatric disorders	-	Depression, insomnia	Anxiety	-
Nervous system disorders	-	Syncope	Somnolence	-
Eye disorders	-	-	Visual disturbance	-
Ear and labyrinth disorders	-	Vertigo	-	-
Cardiac disorders	-	Bradycardia	Tachycardia	-
Vascular disorders	-	Hypotension, orthostatic hypotension	-	-
Respiratory, thoracic and mediastinal	-	Dyspnoea, cough	Interstitial lung disease	-
Gastrointestinal disorders	-	Abdominal pain, diarrhoea, dyspepsia,	Stomach discomfort, dry mouth, dysgeusia	-

		flatulence, vomiting		
Hepato-biliary disorders	-	-	Hepatic function abnormal/liver disorder	-
Skin and subcutaneous tissue disorders	-	Hyperhidrosis, pruritus, rash	Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption	-
Musculoskeletal and connective tissue	-	Myalgia, back pain (e.g. sciatica), muscle spasms	Arthralgia, pain in extremity, tendon pain (tendonitis like symptoms)	-
Renal and urinary disorders	-	Renal impairment including acute renal failure	-	-
General disorders and administration site	-	Chest pain, asthenia (weakness)	Influenza-like illness	-
Investigations	-	Blood creatinine increased	Blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased, haemoglobin decreased	-

Description of selected adverse reactions

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (see section 4.4).

1. Sepsis

In the PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known (see section 5.1).

2. Hypotension

This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.

3. Interstitial lung disease

Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

4. Hepatic function abnormal / liver disorder

Most cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (see section 4.4).

Cilnidipine
Clinically significant adverse reactions
1) Hepatic dysfunction and jaundice (frequency unknown):

Hepatic function disorder and jaundice accompanied with increased AST (GOT), ALT (GPT) and γ-GTP may occur. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of Cilnidipine Tablets, should be taken.

2) Thrombocytopenia (incidence: <0.1%): Since thrombocytopenia may occur, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of Cilnidipine Tablets, should be taken.

If any of the following adverse reactions occur, appropriate measures should be taken depending on the symptoms.

SYSTEM / ORGAN	**0.1 to 5% Incidence**	**<0.1% Incidence**	**Incidence unknown**
Hepatic **Note 1**	Increases in AST (GOT), ALT (GPT), LDH, etc.	ALP increased	
Renal	Increases in creatinine or urea nitrogen, urinary protein positive	Urinary sediment present	
Psychoneurological	Headache, headache dull, dizziness, dizziness on standing up, shoulder muscle stiffness	Sleepiness, insomnia, tremor finger, forgetfulness	Numbness
Gastrointestinal	Nausea, vomiting, abdominal pain	Constipation, bloating, thirst, gingival hypertrophy, heartburn, diarrhea	

Cardiovascular	Flushed face, palpitation, feeling hot, electrocardiogram abnormal (ST depressed, inverted T waves), blood pressure decreased	Chest pain, cardiothoracic ratio increased, tachycardia, atrioventricular block, feeling cold	Extrasystole, bradycardia
Hypersensitivity **Note 2**	Rash	Redness, Itching	Photosensitivity
Hematologic	Up or down in WBC, neutrophils and hemoglobin	Up or down in RBC, haematocrit, eosinophils and lymphocytes	
Other	Oedema (facial, lower leg, etc.), general malaise,	Feelings of weakness, gastrocnemius	Tinnitus

	pollakiuria, increased serum cholesterol, up or down in CK (CPK), uric acid, serum K and serum P	muscle cramps, periophthalmic dryness, ocular hyperemia and feeling of irritation, dysgeusia, urine sugar positive, up or down in fasting blood sugar, total protein, serum Ca and CRP, Cough.	

Note 1): The patient should be carefully monitored for these symptoms, and if any abnormality is noted, Cilnidipine Tablets should be discontinued. Note 2): If any such symptom appears, Cilnidipine Tablets should be discontinued. Inform your doctor of undesirable effects occurred during the use of drug.

Reporting of suspected adverse reactions:
Healthcare professionals are asked to report any suspected adverse reactions ND PQMPs to https://pv.pharmacyboardkenya.org

4.9 Overdose

Telmisartan:
No data available in regard to overdose in humans. If symptomatic hypertension should occur,
supportive treatment should be initiated. Also tachycardia; bradycardia, dizziness, increase in serum
creatinine,and acute renal failure have also been reported. Telmisartan is not removed by
hemodialysis.
Cilnidipine:
Overdose with Cilnidipine may result in excessive peripheral vasodilatation and possibly reflex
tachycardia. Marked and probably prolonged systemic hypotension
up to and including shock with fatal outcome may occur.
Treatment should be symptomatic and supportive. Management depends on the time since ingestion
and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric

lavage. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and
creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a
supine position, with salt and volume replacement given quickly.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Category:

- Angiotensin II Antagonist
- Calcium Antagonist

Mechanism of Action:

Telmisartan

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC Code: C09CA07.

Mechanism of action

Telmisartan is an orally active and specific angiotensin II receptor (type 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.
In human, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

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 to 8 weeks after the start of treatment and is sustained during long-term therapy.
The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure (SBP). In this respect data concerning diastolic blood pressure (DBP) 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 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 (**ON**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial) 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).

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.
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.
Paediatric population
The safety and efficacy of telmisartan in children and adolescents aged below 18 years have not been established.

The blood pressure lowering effects of two doses of telmisartan were assessed in 76 hypertensive, largely overweight patients aged 6 to < 18 years (body weight ≥ 20 kg and ≤ 120 kg, mean 74.6 kg), after taking telmisartan 1 mg/kg (n =29 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. By inclusion the presence of secondary hypertension was not investigated. In some of the investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to 160 mg, which was tested in adults. After adjustment for age group effects mean SBP changes from baseline (primary objective) were -14.5 (1.7) mm Hg in the telmisartan 2 mg/kg group, -9.7 (1.7) mm Hg in the telmisartan 1 mg/kg group, and -6.0 (2.4) in the placebo group. The adjusted DBP changes from baseline were -8.4 (1.5) mm Hg, -4.5 (1.6) mm Hg and -3.5 (2.1) mm Hg respectively. The change was dose dependent. The safety data from this study in patients aged 6 to < 18 years appeared generally similar to that observed in adults. The safety of long term treatment of telmisartan in children and adolescents was not evaluated.
An increase in eosinophils reported in this patient population has not been recorded in adults. Its clinical significance and relevance is unknown.
These clinical data do not allow to make conclusions on the efficacy and safety of telmisartan in hypertensive paediatric population

Cilnidipine
Selective calcium channel blockers with mainly vascular effects – Dihydropyridine derivatives.
ATC code: C08CA14

Cilnidipine is a dihydropyridine calcium channel blocker. It inhibits cellular influx of calcium, thus causing vasodilatation. It has greater selectivity for vascular smooth muscle. Cilnidipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing peripheral vascular residence.

Antihypertensive Effect:
In various hypertensive animal models (spontaneously hypertensive rats, renal hypertensive rats and dogs, DOCA salt hypertensive rats, and stroke-prone spontaneously hypertensive rats), a single oral dose of cilnidipine showed a gradual and long-lasting hypotensive action that was dose-dependent at 1mg/kg or more. In contrast, it showed a weak hypotensive action in normotensive rats. The duration of the action was not prolonged by an excessive dosage.

In renal hypertensive dogs, cilnidipine showed an additive effect when co-administered with a β-blocker or an angiotensin-converting enzyme inhibitor.
In stroke-prone spontaneously hypertensive rats and renally hypertensive dogs, repeated oral doses of cilnidipine had a stable hypotensive action which did not show attenuation. Discontinuation of cilnidipine did not cause a rebound in blood pressure.
In conscious and unrestrained spontaneously hypertensive rats, cilnidipine did not increase the heart rate during hypotension. Cilnidipine did not increase the plasma noradrenaline level during hypotension, nor did it cause a significant decrease, which an adrenergic blocker (guanethidine sulfate) did. Cilnidipine did not cause orthostatic hypotension, although a ganglion blocker (pentolinium) did in a tilt test using rabbits.
In patients with essential hypertension, a single daily dose of cilnidipine showed a hypotensive action that maintained for 24 hours and was still evident early in the next morning. Power spectral analysis of the R-R intervals of 24 hours electrocardiogram revealed that cilnidipine did not increase sympathetic activity or the heart rate as a reflex response to the reduction of blood pressure.
Inhibitory action on Stress induced Pressor Response
In conscious and unrestrained spontaneously hypertensive rats, cilnidipine inhibited the elevation of blood pressure and plasma norepinephrine levels induced by cold stress. Cilnidipine also inhibited the elevation of blood pressure induced by air jet stress (mental stress) in rats. In healthy adult male volunteers whose blood pressure was elevated by 20% or more in cold stress test, cilnidipine suppressed the elevation of blood pressure induced by cold stress.
Inhibitory action on Sympathetic Stimulation induced Pressor Response
In pithed spontaneously hypertensive rats, cilnidipine suppressed the elevation of blood pressure induced by electrical sympathetic stimulation.
In isolated and perfused mesenteric arterial vascular preparation in spontaneously hypertensive rats, cilnidipine also inhibited the release of norepinephrine induced by electrical sympathetic stimulation.

Effect on Cerebral Circulation
In spontaneously hypertensive rats, cilnidipine did not decrease cerebral blood flow even if the dose which decrease blood pressure by 30-40% in rats was administered. The autoregulation of cerebral blood flow was satisfactorily maintained while the blood pressure was decreased.
In hypertensive patients complicated by cerebrovascular disease, the cerebral blood flow was maintained while blood pressure was lowered.

Effects on Cardiac Function
In dogs, cilnidipine decreased heart rate and myocardial contractility at a higher dose than that inducing an increased flow of arterial blood. In anesthetized open chest dogs, cilnidipine decreased the myocardial oxygen consumption at dose inducing hypotension. At the time, it neither caused tachycardia nor affected cardiac contractility. In patients with essential hypertension, cilnidipine did not affect heart rate while the blood pressure was decreased and in patients with abnormal cardiothoracic ratio (CTR), it improved the CTR.

Effects on Renal Function
In anesthetized spontaneously hypertensive rats, cilnidipine increased the urinary volume, renal blood flow and glomerular filtration rate at the dose inducing hypotension. Cilnidipine also increased the urinary volume, renal blood flow and glomerular filtration rate, when the renal function was depressed by endothelin.
In patients with essential hypertension, cilnidipine did not affect renal function while the blood pressure was decreased.

Effect on Cardiovascular Disturbance Associated with Hypertension
In stroke-prone spontaneously hypertensive rats, a single daily dose of cilnidipine suppressed the appearance of stroke and improved the survival rate. In addition, it lessened cardiac hypertrophy (increased heart weight), thickening of the ventricular wall, myocardial fibrosis and lesions in the kidney. Moreover, it depressed medial thickening in the coronary arterial wall and decreased calcium content in the aorta. In patients with essential hypertension, cilnidipine decreased the atherosclerotic index and serum lipid peroxide.

5.2 Pharmacokinetic properties

Telmisartan
Absorption
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.
Linearity/non-linearity
The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.
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 (V_{dss}) is approximately 500 l.

Biotransformation
Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.
Elimination
Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) 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 (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).
Special Populations
Paediatric population
The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to < 18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age related differences. Although the study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for Cmax.
Gender
Differences in plasma concentrations were observed, with C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.
Elderly
The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.
Renal impairment
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations 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 patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.
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.
Cilnidipine

Absorption and distribution*:* Cilnidipine is completely absorbed from the gastrointestinal tract after administration of Cilnidipine extended-release tablets. The systemic availability of Cilnidipine is approximately 15% in man and is independent of dose in the therapeutic dose range. The plasma protein binding of Cilnidipine is approximately 99.3%. It is bound predominantly to the albumin fraction.

Elimination and metabolism: The average half-life of Cilnidipine in the terminal phase is 1.8-2.2 hours. There is no significant accumulation during long-term treatment. Cilnidipine is extensively metabolized by the liver and all identified metabolites are inactive. Elderly patients and patients with reduced liver function have an average higher plasma concentration of Cilnidipine than younger patients. About 70% of a given dose is excreted as metabolites in the urine; the remaining fraction is excreted in the faeces. Less than 0.5% of a dose is recovered unchanged in the urine. The kinetics of Cilnidipine is not changed in patients with renal impairment.

5.3 Preclinical safety data

No additional data of relevance

6. Pharmaceutical Particulars

6.1 List of Excipients

1. Maize Starch
2. Lactose
3. Microcrystalline Sodium
4. Croscarmellose Sodium
5. Povidone (P.V.P.K 30)
6. Isopropyl Alcohol
7. Mannitol
8. Meglumine
9. Ethanol
10. Purified Talc
11. Magnesium Stearate
12. Hypromellose
13. Titanium Dioxide
14. Yellow Oxide of Iron
15. Red Oxide of Iron
16. Dichloromethane

6.2 Incompatibilities

None Reported

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store below 30°C. Protect from direct sunlight, heat and moisture. Keep all medicines out of reach of children.

6.5 Nature and Content of container
Blister pack of 3 x 10 tablets

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements**.**

7. Marketing Authorization Holder
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8. Marketing Authorization Number
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9. Date of first authorization/renewal of the authorization
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10. Date of revision of the text
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