Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Cilnidipine & Telmisartan Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Cilnidipine	5 mg
Telmisartan USP	40 mg

Excipients with known effect:

Dichloromethane

For a full list of excipients see section 6.1

3. Pharmaceutical form

Film coated tablet.

A yellow coloured, round in Shape, biconvex, film coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

CILVAS TEL Tablets are indicated for the treatment of essential hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily stroke and myocardial infarction (MI).

CILVAS TEL Tablets are usually administered in patients whose blood pressure is not adequately controlled by monotherapy with either telmisartan or cilnidipine.

CILVAS TEL Tablets may be used alone or in combination with other antihypertensive drugs.

4.2 Posology and method of administration

Posology

The usual dose is 1 tablet of CILVAS TEL to be administered once daily. Adjust dosage according to blood pressure goals. If adequate response is not achieved after 2 to 4 weeks of therapy, dose may be increased to 2 tablets once daily. The dosage, however, must be individualized.

Dosage of individual agents should not exceed the recommended maximum daily doses.

-Cilnidipine is effective over the range of 5 to 20 mg once daily; maximum recommended daily dose is 20mg.

-Telmisartan efficacy is dose-related over the range of 20 to 80 mg per day; maximum recommended daily dose is 80 mg.

If blood pressure remains uncontrolled, consider a change to more appropriate treatment.

Method of administration
For oral administration in adults.
CILVAS TEL Tablets can be administered regardless of meal. The tablet should be swallowed whole with water.

4.3 Contraindications

CILVAS TEL Tablets are contraindicated in the following conditions:
-Hypersensitivity to cilnidipine or to telmisartan or to any component of the formulation. -Cardiogenic shock.
-Severe aortic stenosis.
-Recent history of unstable angina or acute myocardial infarction, heart failure, hypotension.
-Second and third trimesters of pregnancy.
-Severe hepatic impairment and biliary obstructive disorders.
-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).

4.4 Special warnings and precautions for use

Cilnidipine
Cardiovascular Disorders: Cilnidipine should be used with caution in patients with hypotension, heart failure, and poor cardiac reserve. Cilnidipine should be discontinued immediately in patients who feel chest pain following the administration of the drug.
Abrupt Cessation of Therapy: In case of angina, cilnidipine should not be discontinued abruptly to avoid withdrawal symptoms.
Grapefruit Juice: Grapefruit juice may intensify the effect of cilnidipine. Thus, avoid drinking grapefruit juice as much as possible while on cilnidipine therapy.
Laboratory Test: Cilnidipine therapy may interfere with the results of vanillyl mandelic acid test which is used to detect tumors such as pheochromocytoma and neuroblastoma.
Therefore, cilnidipine should be avoided for 72 hours before sample collection, but the patient should be monitored intensively in a clinical setting.
Liver dysfunction or elevated liver enzymes
Peripheral edema (confounding physical findings in congestive failure)
Pregnancy – There are no human clinical or animal data concerning the safety of
Cilnidipine during pregnancy & therefore use during pregnancy should be avoided.

Telmisartan

Fetal Toxicity: Use of drugs that act on the RAAS during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death.
Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. Thus, when pregnancy is detected, discontinue telmisartan as soon as possible.

Hypotension: In patients with an activated RAAS, such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with telmisartan. Either correct this condition prior to administration of telmisartan, or start treatment under close medical supervision with a reduced dose.

Hyperkalemia: Hyperkalemia may occur in patients on angiotensin receptor blockers/antagonists (ARBs), particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

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 drugs that affect the RAAS.

Dual Blockade of the RAAS: There is evidence that the concomitant use of angiotensin converting enzyme
(ACE) inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through combined use of ACE-inhibitors, ARBs or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and be subject to close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. Do not co-administer aliskiren with telmisartan in patients with diabetes or renal impairment.

Other Body Functions Depends on the Activation of RAAS: As a consequence of inhibiting the RAAS, changes in renal function in susceptible individuals may be anticipated.
In patients whose vascular tone and renal function depend predominantly on the activity of the RAAS (e.g., patients with severe congestive heart failure or underlying renal disease, including renal

artery stenosis), treatment with drugs which affect this system such as telmisartan has been associated with acute hypotension, azotemia, oliguria, or rarely acute renal failure.

Primary Aldosteronism*:* Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the RAAS. Therefore, 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 Antidiabetic Drugs:
Hypoglycaemia may occur when telmisartan is co-administered with these drugs. Therefore, in these patients appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

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

4.5 Interaction with other medicinal products and other forms of interaction

Cilnidipine
Antipsychotic Drugs: Co-administration of antipsychotic drugs with cilnidipine may result in low blood pressure. Thus, caution should be exercised while concomitant use of these drugs with cilnidipine.
Antidiabetic Drugs: Co-administration of cilnidipine with antidiabetic drugs may result in changes in glucose levels, thus, monitoring of blood glucose levels may be required.
Other Drugs: Antiepileptic drugs (such as phenytoin and carbamazepine), rifampin, quinidine, erythromycin, other anti-hypertensive drugs, and aldesleukin should also be used with caution along with cilnidipine.

Telmisartan

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.
As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia (see section 4.4). The risk may increase in case of treatment combination with other

medicinal products that may also provoke hyperkalaemia (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).
The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.
Concomitant use not recommended
Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.
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 agents 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.
In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.
Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume

depletion, and in a risk of hypotension when initiating therapy with telmisartan.

To be taken into account with concomitant use

Other antihypertensive agents

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

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic use)

Reduction of the antihypertensive effect.

Aliskiren: Do not co-administer aliskiren with telmisartan in patients with diabetes. Avoid use of aliskiren with telmisartan in patients with renal impairment (GFR < 60 ml/min/1.73 m2).

4.6 Pregnancy and Lactation

Pregnant Women

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Thus, pregnant women with hypertension should be carefully monitored and managed accordingly.

The safety of cilnidipine in human pregnancy has not been established. Telmisartan causes fetal harm when administered to a pregnant woman. Use of drugs that act on the reninangiotensin aldosterone system (RAAS) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Thus, CILVAS TEL Tablets are contraindicated during the second and third trimesters of pregnancy. When pregnancy is detected or planned, CILVAS TEL Tablets should be discontinued immediately and appropriate alternative therapy should be initiated.

Lactating Women

It is not known whether cilnidipine is secreted in breast milk. There is no information regarding the presence of 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. Telmisartan has potential for serious adverse reactions including hypotension, hyperkalemia, and renal impairment in the breastfed infant. Thus, it is

advisable that nursing mothers not breastfeed their children while on CILVAS TEL therapy. Accordingly, a decision should be made whether to discontinue nursing or discontinue drug therapy, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

For cilnidipine and telmisartan combination therapy, studies have not been performed on effects on the ability to drive and use machines. It is advised not to operate machinery or drive a vehicle if patient experience side effects such as drowsiness, dizziness, fatigue, headache, or hypotension while taking antihypertensive drug therapy.

4.8 Undesirable effects

Cilnidipine

Dizziness, headache, peripheral edema, flushing, rash and gingival hyperplasia are the
most common adverse events seen with the dihydropyridine derivative calcium channel
antagonists. Headache, flushing was reported in 3.7 & 4.5 % of 764 subjects receiving
Cilnidipine respectively.

Telmisartan

Summary of the safety profile

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.

Infections and infestations
Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis
Rare: Sepsis including fatal outcome[1]
Blood and the lymphatic system disorders
Uncommon: Anaemia
Rare: Eosinophilia, thrombocytopenia
Immune system disorders
Rare: Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders
Uncommon: Hyperkalaemia
Rare: Hypoglycaemia (in diabetic patients)
Psychiatric disorders
Uncommon: Depression, insomnia
Rare: Anxiety
Nervous system disorders
Uncommon: Syncope
Rare: Somnolence
Eye disorders
Rare: Visual disturbance
Ear and labyrinth disorders
Uncommon: Vertigo
Cardiac disorders
Uncommon: Bradycardia
Rare: Tachycardia
Vascular disorders
Uncommon: Hypotension[2], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough
Very rare: Interstitial lung disease[3]
Gastrointestinal disorders
Uncommon: Abdominal pain, diarrhoea, dyspepsia , flatulence, vomiting
Rare: Stomach discomfort, dry mouth, dysgeusia
Hepato-biliary disorders
Rare: Hepatic function abnormal/liver disorder[4]
Skin and subcutaneous tissue disorders
Uncommon: Hyperhidrosis, pruritus, rash
Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Muscoloskeletal and connective tissue disorders
Uncommon: Myalgia, back pain (e.g. sciatica), muscle spasms
Rare: Arthralgia, pain in extremity, tendon pain (tendonitis like symptoms)
Renal and urinary disorders
Uncommon: Renal impairment including acute renal failure
General disorders and administration site conditions
Uncommon: Chest pain, asthenia (weakness)
Rare: Influenza-like illness
Investigations

Uncommon: Blood creatinine increased
Rare: Blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased, haemoglobin decreased
1,2,3,4: for further descriptions, please see sub-section *"Description of selected adverse reactions"*
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).
Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Cilnidipine
In humans, experience with cilnidipine overdose is limited. Overdose symptoms include confusion, dizziness, headache, fatigue, and sedation. If overdose occurs, it might cause excessive peripheral vasodilation with marked hypotension.
If 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.
Telmisartan

There is limited information available with regard to overdose in humans.

Symptoms: The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.
Treatment: Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose. 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

Cilnidipine

Mechanism of Action:

1. Cilnidipine is a third-generation dihydropyridine calcium antagonist with a slow onset
and long duration of action. Calcium antagonists inhibit influx of extracellular calcium ions
into the cells, resulting in decreased vascular smooth muscle tone and vasodilation, leading
to a reduction in blood pressure. The dihydropyridine derivatives (cilnidipine, amlodipine,
nisoldipine, nifedipine, felodipine, nitrendipine, nimodipine) differ from the
benzothiazepine (eg, diltiazem) and phenylalkylamine (eg, verapamil) classes of calcium
antagonists with regard to potency, tissue selectivity, and antiarrhythmic effects. In general,
dihydropyridine agents are the most potent arteriolar vasodilators, producing the least
negative inotropic and electrophysiologic effects; in contrast, verapamil and diltiazem slow
atrioventricular (AV) conduction and exhibit negative inotropic activity while also
maintaining some degree of arteriolar vasodilatation (Katz & Leach, 1987).
2. In vitro and animal studies suggest that cilnidipine blocks both the L- and N- type
calcium channels. Cilnidipine inhibits the pressor response to cold stress by suppressing
sympathetic nerve activity in spontaneously hypertensive rats. It does not induce
tachycardia caused by hypotensive baroreflexes. In vitro, cilnidipine inhibits
norepinephrine release in electrically stimulated rabbit mesenteric arteries (Saruta, 1998).

3. In human studies, cilnidipine had weak inotropic effects and suppressed cardiac
sympathetic over activity. Therefore, it may decrease the risk and mortality from longterm
cardiovascular complications (Sakata et al, 1999). Once-daily cilnidipine was associated
with less reflex tachycardia and had fewer effects on the autonomic nervous system than
sustained-release nifedipine in hypertensive patients (Minami et al, 1998a; Minami et al,
2000). In contrast to other long-acting calcium channel blockers, cilnidipine and
amlodipine did not increase plasma renin activity, thus they may decrease the risk of
cardiovascular complications due to metabolic imbalances (Sakata et al, 1999). Cilnidipine
may inhibit norepinephrine and dopamine production, thereby improving insulin resistance
in patients with diabetes (Takeda et al, 1999). It also had beneficial effects on lipid profiles
in hypertensive patients by decreasing total cholesterol, triglyceride, and very low density
lipoprotein cholesterol levels, and increasing high density lipoprotein cholesterol and the
ratio of high-density lipoprotein cholesterol to total cholesterol (Ahaneku et al, 2000)

Telmisartan

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.

5.2 Pharmacokinetic properties

Cilnidipine

Absorption: After oral administration of cilnidipine, absorption is very rapid with peak plasma concentration reached after 2 hours.

Distribution: Distribution of cilnidipine tends to be higher in the liver as well as in kidneys, plasma, and other tissues. Cilnidipine has a large volume of distribution. Plasma protein binding of cilnidipine is very high i.e., 98% of the administered dose.

Metabolism: Cilnidipine is metabolized by both liver and kidney. It is rapidly metabolized by liver microsomes by a dehydrogenation process. The major enzymatic isoform involved in cilnidipine dehydrogenation of the dihydropyridine ring is CYP3A.

Excretion: Approximately 20% of the administered dose of cilnidipine gets eliminated through the urine, with the remainder (about 80%) being eliminated in feces.

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.

5.3 Preclinical safety data

Cilnidipine

No relevant information available.

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 sodium chloride solution 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 offsprings such as lower body weight and delayed eye opening was observed.

There was no evidence of mutagenicity and relevant clastogenic activity in *in vitro* studies and no evidence of carcinogenicity in rats and mice.

6. Pharmaceutical Particulars

6.1 List of Excipients

Polysorbate-80 (Tween 80), Sodium Hydroxide, Microcrystalline Cellulose Powder (MCCP), Colloidal Anhydrous Silica, Crospovidone, Magnesium stearate, Purified-Water, Purified Talc, Polacrilin Potassium, Microcrystalline Cellulose Powder-102, Sodium starch glycolate, Film Coat (Sun coat), Yellow Oxide of iron, Titanium Dioxide, Iso Propyl Alcohol (IPA) and Dichloromethane (MDC).

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store below 30°C and protect from direct sunlight.

6.5 Nature and Content of container

2 x 14 pack: 14 tablets packed in Alu-Alu blister and such 2 Alu-Alu blisters are packed in single carton along with pack insert.

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing Authorization Holder
FREDUN PHARMACEUTICALS LIMITED

8. Marketing Authorization Number
CTD9503

9. Date of first authorization/renewal of the authorization
18/04/2024

10. Date of revision of the text
5/16/2025