

## **1.6 Product Information**

### **1.6.1 Prescribing Information**

#### **(SUMMARY OF PRODUCT CHARACTERISTICS)**

#### **Name of the Finished Pharmaceutical Product**

##### **1- Product name**

T-Sar Tablet 40mg

##### **1.1 Strength**

40mg

##### **1.2 Pharmaceutical form**

Tablet

#### **2- Qualitative and Quantitative Composition**

##### **2.1 Qualitative Declaration**

Telmisartan

##### **2.2 Quantitative Declaration**

Each tablet contains:

Telmisartan.....40mg

#### **3- Pharmaceutical Form**

Light green colored round biconvex shaped tablet

#### **4- Clinical Particulars:**

##### **4.1 Therapeutic Indications**

###### **Hypertension**

Treatment of essential hypertension in adults

###### **Cardiovascular prevention**

Reduction of cardiovascular morbidity in adults with:

- Manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or
- Type 2 diabetes mellitus with documented target organ damage.

## **.2 Posology and Method of Administration**

### **Posology**

#### **Treatment of essential hypertension**

The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 80 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily. Alternatively, telmisartan may be used in combination with thiazidetype diuretics such as hydrochlorothiazide which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

#### **Cardiovascular prevention**

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing cardiovascular morbidity.

When initiating telmisartan therapy for the reduction of cardiovascular morbidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

### **Special populations**

#### **Patients with renal impairment**

Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of 80 mg is recommended in these patients. No posology adjustment is required for patients with mild to moderate renal impairment.

#### **Patients with hepatic impairment**

Telmisartan Actavis is contraindicated in patients with severe hepatic impairment  
In patients with mild to moderate hepatic impairment the posology should not exceed 40 mg once daily.

#### **Elderly patients**

No dose adjustment is necessary for elderly patients.

#### **Paediatric population**

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

## **4.3 Method of administration**

Telmisartan tablets are for once-daily oral administration and should be taken with liquid, with or without food.

## **4.4 Contra Indications**

- Hypersensitivity to the active substance or to any of the excipients
- Second and third trimesters of pregnancy
- Biliary obstructive disorders
- Severe hepatic impairment

The concomitant use of Telmisartan Actavis with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m<sup>2</sup>).

#### **4.5 Special warning and precautions for use**

##### **WARNINGS:**

##### **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 Actavis is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment (see section 4.3) since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Telmisartan Actavis 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 renin-angiotensin-aldosterone system.

##### **Renal impairment and kidney transplantation**

When Telmisartan Actavis 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 Actavis in patients with recent kidney transplantation.

##### **Intravascular hypovolaemia**

Symptomatic hypotension, especially after the first dose of Telmisartan Actavis, 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 Actavis. Volume and/or sodium depletion should be corrected prior to administration of Telmisartan Actavis.

##### **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 renin-angiotensin-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 renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic class 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, 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 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.

## **4.6 Drug interactions**

### **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. spironolactone, 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 nonselective 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.

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 route)**

Reduction of the antihypertensive effect.

## **4.7 Undesirable effects:**

### **Summary of the safety profile**

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely ( $\geq 1/10,000$  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 placebo 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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: Urinary tract infection including cystitis, upper respiratory tract  
Rare: infection including pharyngitis and sinusitis  
Sepsis including fatal outcome<sup>1</sup>

##### 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: Insomnia, depression  
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<sup>2</sup>, orthostatic hypotension

#### Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, cough  
Very rare: Interstitial lung disease<sup>4</sup>

#### Gastrointestinal disorders

Uncommon: Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting  
Rare: Dry mouth, stomach discomfort, dysgeusia

#### Hepato-biliary disorders

Rare: Hepatic function abnormal/liver disorder<sup>3</sup>

#### Skin and subcutaneous tissue disorders

Uncommon: Pruritus, hyperhidrosis, rash  
Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption

#### Musculoskeletal and connective tissue disorders

Uncommon: Back pain (e.g. sciatica), muscle spasms, myalgia  
Rare: Arthralgia, pain in extremity, tendon pain (tendinitis 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: Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

#### **4.8 Effects on ability to drive and operate machine:**

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as Telmisartan Actavis

#### **4.9 Overdoses:**

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.

### 3- PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties:

##### ATC classification

Angiotensin II Antagonists

**ATC code:** C09CA07

##### Mechanism of Action

Telmisartan is an orally active and specific angiotensin II receptor (type AT<sub>1</sub>) antagonist.

Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT<sub>1</sub> receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT<sub>1</sub> receptor. Telmisartan selectively binds the AT<sub>1</sub> receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT<sub>2</sub> and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan.

Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects.

In 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**

**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 **H**eart **O**utcomes **P**revention **E**valuation 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. 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.

### **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  $\geq$  20 kg and  $\leq$  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:**

### **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  $C_{max}$ .

#### **Gender**

Gender differences in plasma concentrations were observed,  $C_{max}$  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 Pre-clinical safety data:**

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 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**

- Mannitol
- Kollidon K-30 (Polyvinylpyrrolidone/Povidone)
- Croscarmellose Sodium
- Potassium Hydroxide
- Magnesium Stearate
- Color Green Lake
- Isopropyl Alcohol

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf-Life**

2 years

### **6.4 Special Precautions for Storage**

- Stored below 30°C.
- Protect from heat sunlight and moisture
- Keep away from heat, moisture, light and children

### **6.5 Nature and Contents of Container**

3x10's tablets packed in Alu-Alu blister, in bleach board unit carton with leaflet.

### **6.6 Special Precautions for Disposal and other Handling**

Not applicable

### **7- Marketing Authorization Holder and Manufacturing Site Address**

Name: CCL Pharmaceuticals (Pvt.) Ltd.  
Address: 62-Industrial Estate, Kot Lakhpat, Lahore-54770, Pakistan.  
Telephone: +92-42-5114753  
Fax: +92-42-35114382  
E-mail: [mail.ccl@cclpharma.com](mailto:mail.ccl@cclpharma.com),

### **8- Marketing Authorization Number**

EX-001743

### **9- Date of First Authorization / Renewal of Authorization**

Date of first authorization	29-11-2012
Date of next renewal	29-11-2017

### **10- Date of Revision Of The Text**

27-06-2016