

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1.15.1 Product information for Health Professionals**

**(For All Products Subject to Medical Prescription)**

**1. Name of the Medicinal Product**

**1.1 Product Name**

ZYTEL 80 (Telmisartan Tablets BP, 80 mg)

**1.2 Strength**

Telmisartan BP 80 mg/Tablet

**1.2.1 Pharmaceutical Dosage Form**

Solid Dosage Form (Uncoated Tablets)

**2. Qualitative and Quantitative Composition**

**2.1.1 Qualitative Declaration**

**Composition:**

Each uncoated tablet contains:

Telmisartan BP.....80 mg

Excipients .....q.s.

**2.2 Quantitative Declaration**

**Batch Formula: 1,00,000 Tablets**

| Sr. No.                        | Material Name                             | Spec. | Quantity (mg)/ Tablet | % Formula w/w | Theoretical Quantity / Batch (kg) | Ovg. in %/# | Standard Quantity / Batch ( kg) |
|--------------------------------|-------------------------------------------|-------|-----------------------|---------------|-----------------------------------|-------------|---------------------------------|
| <b>Dry Mixing</b>              |                                           |       |                       |               |                                   |             |                                 |
| 01                             | Microcrystalline Cellulose (101)**        | BP    | 201.800               | 44.844        | 20.180                            | .....       | 20.180                          |
| 02                             | Mannitol                                  | BP    | 54.000                | 12.000        | 5.400                             | .....       | 5.400                           |
| 03                             | Crospovidone (XL-10) (Polyplasdone XL-10) | BP    | 20.000                | 4.444         | 2.000                             | .....       | 2.000                           |
| <b>Preparation of solution</b> |                                           |       |                       |               |                                   |             |                                 |

|                              |                                                  |    |                |            |               |             |               |
|------------------------------|--------------------------------------------------|----|----------------|------------|---------------|-------------|---------------|
| 04                           | Telmisartan*                                     | BP | 81.210         | 18.047     | 8.121         | .....       | 8.121         |
| 05                           | Sodium Hydroxide (Pellets)                       | BP | 8.000          | 1.778      | 0.800         | .....       | 0.800         |
| 06                           | Polysorbate-80                                   | BP | 2.000          | 0.444      | 0.200         | .....       | 0.200         |
| 07                           | Isopropyl Alcohol                                | BP | .....          | ....       | 6.400         | .....       | 6.400         |
| 08                           | Purified water                                   | BP | .....          | ....       | 4.000Ltrs     | ....        | 4.000Ltrs     |
| <b>Blending/ Lubrication</b> |                                                  |    |                |            |               |             |               |
| 09                           | Crospovidone (XL-10) (Polypasdone XL-10)         | BP | 20.000         | 4.444      | 2.000         | .....       | 2.000         |
| 10                           | Sodium Starch Glycolate (Primojel)               | BP | 13.500         | 3.000      | 1.350         | .....       | 1.350         |
| 11                           | Croscarmellose Sodium (Ac-Di-Sol)                | BP | 13.500         | 3.000      | 1.350         | .....       | 1.350         |
| 12                           | Microcrystalline Cellulose (PH-102) (Avicel 102) | BP | 27.000         | 6.000      | 2.700         | .....       | 2.700         |
| 13                           | Colloidal Silicon Dioxide                        | BP | 4.500          | 1.000      | 0.450         | .....       | 0.450         |
| 14                           | Magnesium Stearate                               | BP | 4.500          | 1.000      | 0.450         | .....       | 0.450         |
| <b>TOTAL</b>                 |                                                  |    | <b>450.000</b> | <b>100</b> | <b>45.000</b> | <b>....</b> | <b>45.000</b> |

*\*Standard quantity 8.121 kg has been calculated based on 99.00 % assay (approx.) of Telmisartan on “on dried basis” & Standard LOD 0.5 % w/w.*

*\*\*Note: Adjust the qty. of Microcrystalline Cellulose (101) depending upon the quantity of Telmisartan used.*

### **3. Pharmaceutical Form**

Solid Dosage Form (Uncoated Tablets)

### **4. Clinical Particular**

#### **4.1 Therapeutic indications**

**ZYTEL 80** is indicated for

#### **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.

#### **4.2 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 20 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 thiazide-type 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 20 mg is recommended in these patients . No posology adjustment is required for patients with mild to moderate renal impairment.

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

Telmisartan 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 have not been established. Currently available data are described and but no recommendation on a posology can be made.

### **Method of administration**

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

Precautions to be taken before handling or administering the medicinal product.

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

### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients of the formulation.
- Second and third trimesters of pregnancy
- 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 m<sup>2</sup>) .

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

#### **Pregnancy**

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started .

#### **Hepatic impairment**

Telmisartan is 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 renin-angiotensin-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 hypoglycemia 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 classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.
- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma).

Close monitoring of serum potassium in at risk patients is recommended (see section 4.5).

### **Sorbitol**

This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Telmisartan.

### **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.

#### **4.5 Interaction with other medicinal products and other forms of 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<sub>0-24</sub> and C<sub>max</sub> 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.

#### **4.6 Fertility, pregnancy and lactation**

**Pregnancy:** The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy . The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy .

There are no adequate data from the use of telmisartan in pregnant women. Studies in animals have shown reproductive toxicity .Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of drugs.

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). . Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension .

### **Breast-feeding**

Because no information is available regarding the use of [To be completed nationally] during breast-feeding, [To be completed nationally] is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

### **Fertility**

In preclinical studies, no effects of telmisartan on male and female fertility were observed.

#### **4.7 Effects on ability to drive and use 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.

#### **4.8 Undesirable effects**

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

Serious adverse drug 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 reaction 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 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.

|                                                        |                                                                                                                   |
|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| <b>Infections and infestations</b>                     |                                                                                                                   |
| Uncommon:                                              | Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis |
| Rare:                                                  | Sepsis including fatal outcome                                                                                    |
| <b>Blood and the lymphatic system disorders</b>        |                                                                                                                   |
| Uncommon:                                              | Anaemia                                                                                                           |
| Rare:                                                  | Eosinophilia , thrombocytopenia                                                                                   |
| Immune system disorders                                |                                                                                                                   |
| Rare:                                                  | Anaphylactic reaction, hypersensitivity                                                                           |
| <b>Metabolism and nutrition disorders</b>              |                                                                                                                   |
| Uncommon:                                              | Hyperkalaemia                                                                                                     |
| Rare:                                                  | Hypoglycaemia (in diabetic patients)                                                                              |
| <b>Psychiatric disorders</b>                           |                                                                                                                   |
| Uncommon:                                              | Insomnia, depression,                                                                                             |
| Rare:                                                  | Anxiety                                                                                                           |
| <b>Nervous system disorders</b>                        |                                                                                                                   |
| Uncommon:                                              | Syncope                                                                                                           |
| Rare:                                                  | Somnolence                                                                                                        |
| <b>Eye disorders</b>                                   |                                                                                                                   |
| Rare:                                                  | Vision disturbance                                                                                                |
| <b>Eye and labyrinth disorders</b>                     |                                                                                                                   |
| Uncommon:                                              | Vertigo                                                                                                           |
| <b>Cardiac disorders</b>                               |                                                                                                                   |
| Uncommon:                                              | Bradycardia                                                                                                       |
| Rare:                                                  | Tachycardia                                                                                                       |
| <b>Vascular disorders</b>                              |                                                                                                                   |
| Uncommon:                                              | Hypotension, orthostatic hypotension                                                                              |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                                                                                                                   |
| Uncommon:                                              | Dyspnoea                                                                                                          |
| Very rare:                                             | Interstitial lung disease                                                                                         |

|                                                             |                                                                                                                    |
|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>Gastrointestinal disorders</b>                           |                                                                                                                    |
| Uncommon:                                                   | Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting                                                         |
| Rare:                                                       | Dry mouth, stomach discomfort, dysgeusia                                                                           |
| <b>Hepato-biliary disorders</b>                             |                                                                                                                    |
| Rare:                                                       | Hepatic function abnormal/liver disorder                                                                           |
| <b>Skin and subcutaneous tissue disorders</b>               |                                                                                                                    |
| Uncommon:                                                   | Pruritus, hyperhidrosis, rash                                                                                      |
| Rare:                                                       | Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption              |
| <b>Musculoskeletal and connective tissue disorders</b>      |                                                                                                                    |
| Uncommon:                                                   | Back pain (e.g. sciatica), muscle spasms, myalgia                                                                  |
| Rare:                                                       | Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)                                              |
| <b>Renal and urinary disorders</b>                          |                                                                                                                    |
| Uncommon:                                                   | Renal impairment including acute renal failure                                                                     |
| <b>General disorders and administration site conditions</b> |                                                                                                                    |
| Uncommon:                                                   | Chest pain, asthenia (weakness)                                                                                    |
| Rare:                                                       | Influenza-like illness                                                                                             |
| <b>Investigations</b>                                       |                                                                                                                    |
| Uncommon:                                                   | Blood creatinine increased                                                                                         |
| Rare:                                                       | Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased |

### **Description of selected adverse reactions**

#### **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 .

#### **Hypotension**

This adverse drug 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.

### **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.

### **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.

## **4.9 Overdose**

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

In case of accidental overdosage the treatment should be symptomatic & supportive.

## **5. Pharmacological Properties**

### **5.1 Pharmacodynamics Properties**

**Pharmacotherapeutic group:** Pharmacotherapeutic group: 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.

## **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).

### **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**

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**

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**

Microcrystalline Cellulose (101), Mannitol , Crospovidone (XL-10) (Polyplasdone XL-10), Sodium Hydroxide (Pellets), Polysorbate-80, Isopropyl Alcohol, Purified water, Sodium Starch Glycolate (Primojel), Croscarmellose Sodium (Ac-Di-Sol), Microcrystalline Cellulose (PH-102) (Avicel 102), Colloidal Silicon Dioxide, Magnesium Stearate.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

24 months from the date of manufacturing.

### **6.4 Special precaution for storage**

Store at a temperature below 30<sup>0</sup>C. Protect from light & moisture.

### **6.5 Nature and content of container**

10 tablets packed in Alu/Alu blister and such 03 blisters packed in a printed mono carton with insert.

### **6.6 Special precaution for disposal**

No special requirements.

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

## **7 Registrant**

**Company name : Cadila Healthcare Limited.**

**Name : Mr. Gaurav**

**Address : Zydus Tower, Satellite Cross Roads,  
Ahmedabad- 380015, India**

### **Manufacturer**

**Company name : EAST AFRICAN (INDIA) OVERSEAS**

**Address : Plot no. 1, Pharmacity, Selaqui  
Dehradun – 248011,  
Uttarakhand (India)**

**8**      **Date of revision of text**

-----

**9**      **Dosimetry (If applicable)**

-----

**10**     **Instruction for preparation of Radiopharmaceuticals (If Applicable)**

-----