SUMMARY OF PRODUCT CHARACTERISTICS

TELFOCUS 40 & 80

Telmisartan Tablets 40 mg & 80 mg

Rx Only

1. NAME OF THE MEDICINAL PRODUCT:

Telmisartan Tablets 40 mg.
Telmisartan Tablets 80 mg.

(TRADE) NAME OF THE PRODUCT:

TELFOCUS 40
TELFOCUS 80

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TELFOCUS 40 mg Tablets. Each Uncoated Tablet Contains Telmisartan Ph.Eur. 40 mg.
TELFOCUS 80 mg Tablets. Each Uncoated Tablet Contains Telmisartan Ph.Eur. 80 mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TELFOCUS 40 mg Tablets:
White to off-white, Oblong shaped, biconvex uncoated tablets, debossed with 'N & 40' on either side of the score line on one side and Plain on the other side.

TELFOCUS 80 mg Tablets:
White to off-white, Oblong shaped, biconvex uncoated tablets, debossed with 'N & 80' on either side of the score line on one side and Plain on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.
Reduction of the risk of non-fatal stroke or non-fatal myocardial infarction in patients 55 years or older at high risk of developing major cardiovascular events who cannot tolerate an angiotensin coverting enzyme inhibitor (ACEI).
High risk of cardiovascular events includes evidence of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or diabetes mellitus with evidence of end-organ damage.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Adults

Treatment of essential hypertension
The recommended 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, telmisartan dose 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 - eight weeks after the start of treatment.
In patients with severe hypertension treatment with telmisartan at doses up to 160 mg alone and in combination with hydrochlorothiazide 12.5 - 25 mg daily was well tolerated and effective.

Reduction of cardiovascular morbidity
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, monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Method of administration
TELFOCUS may be taken with or without food.

Renal impairment
No posology adjustment is required for patients with renal impairment, including those on haemodialysis
Telmisartan is not removed from blood by hemofiltration.

Hepatic impairment
In patients with mild to moderate hepatic impairment the posology should not exceed 40 mg once daily.

Elderly
No dosing adjustment is necessary.

Children and adolescents
TELFOCUS is not recommended for use in children below 18 years due to limited data on safety and efficacy.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy (see section 4.4 and 4.6).
- Biliary obstructive impairment.
- Severe hepatic impairment

The concomitant use of TELFOCUS with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60mg/min/1.73 m^2) see sections 4.5 and 5.1)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pregnancy:
Angiotensin II receptor antagonists should not be initiated during pregnancy.
Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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.

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 transplant:
When TELFOCUS is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of TELFOCUS in patients with a recent kidney transplant.

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

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 (see Interactions).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions with stimulation of the renin-angiotensin-aldosterone system:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of TELFOCUS 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.

Hyperkalaemia:
During treatment with medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with Telmisartan.

Hepatic impairment:
Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. TELFOCUS should be used with caution in these patients.

Diabetes mellitus:
In diabetic patients with an additional cardiovascular risk, i.e. patients with diabetes mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with TELFOCUS.

Other:
As observed for angiotensin converting enzyme inhibitors, angiotensin receptor blockers including TELFOCUS 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.
As with any antihypertensive agent, excessive reduction blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Warning: Fetal/Neonatal Morbidity and Mortality
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, TELFOCUS tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patients discontinue the use of Telmisartan tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Telmisartan tablets should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NTS), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may be appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of TELFOCUS tablets in pregnant women. No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 6.4 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m^2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

TELFOCUS may increase the hypotensive effect of other antihypertensive agents. Other interactions of clinical significance have not been identified.

Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (39% in a single case), monitoring of plasma digoxin levels should be considered.

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.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors.

Cases have also been reported with angiotensin II receptor antagonists including TELFOCUS. Therefore, serum lithium level monitoring is advisable during concomitant use.

Treatment with NSAIDs (i.e ASA at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDS) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the Renin-Angiotensin-System like telmisartan may have synergistic effects. Patients receiving NSAIDs and TELFOCUS should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.

A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

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 Contraindications and Warnings/ Precautions).

4.6 FERTILITY, PREGNANCY AND LACTATION

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

Angiotensin II receptor antagonists exposure 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).

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

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.

TELFOCUS is contraindicated during lactation since it is not known whether it is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk.

Fertility:
No studies on fertility in humans have been performed.
In preclinical studies, an effect of TELFOCUS on male and female fertility was not observed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 TELFOCUS.

4.8 UNDESIRABLE EFFECTS

The overall incidence of adverse events reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in controlled clinical trials in patients treated for hypertension. The incidence of adverse events was not dose related and showed no correlation with gender, age or race of the patients.
The safety profile of TELFOCUS in patients treated for reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.
The adverse drug 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 events and adverse events leading to discontinuation reported in three clinical long-term studies including 21642 patients treated with telmisartan for reduction of cardiovascular morbidity for up to six years.

Infections and infestations:
Urinary tract infections (including cystitis), upper respiratory tract infections, sepsis including fatal outcome

Blood and lymphatic system disorders:
Anaemia, eosinophilia, thrombocytopenia

Immune system disorders:
Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders:
Hyperkalaemia, hypoglycaemia (in diabetic patients)

Psychiatric disorders:
Insomnia, depression, anxiety

Nervous system disorders:
Syncope (faint)

Eye disorders:
Visual disturbance

Ear and labyrinth disorders:
Vertigo

Cardiac disorders:
Bradycardia, tachycardia

Vascular disorders:
Hypotension, orthostatic hypotension

Respiratory disorders:
Dyspnoea

Gastro-intestinal disorders:
Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dry mouth, stomach discomfort.

Hepatobiliary disorders:
Hepatic function abnormal / liver disorder*
*Most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in patients in Japan.

Skin and subcutaneous tissue disorders:
Pruritus, hyperhidrosis, rash, angioedema (with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders:
Back pain, muscle spasms (cramps in legs), myalgia, arthralgia, pain in extremity (leg pain), tendon pain (tendinitis like symptoms)

Renal and urinary tract disorders:
Renal impairment including acute renal failure (see also under Special precautions and warnings)

General disorders and administration site conditions:
Chest pain, asthenia (weakness), influenza-like illness

Investigations:
Blood creatinine increased, haemoglobin decreased, blood uric acid increased, hepatic enzymes increased, blood creatine phosphokinase (CPK) increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: pharmacovigilance@aurobindo.com.

4.9 OVERDOSE
Limited information is available with regard to overdose in humans. The most prominent manifestations of telmisartan overdose were hypotension and tachycardia, bradycardia also occured. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by haemodialysis.

5.0 PHARMACOLOGICAL PROPERTIES

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

MECHANISM OF ACTION
Telmisartan is an orally active and specific angiotensin ii receptor (type at1) antagonist. Telmisartan displaces angiotensin ii with very high affinity from its binding site at the at1 receptor subtype, which is responsible for the known actions of angiotensin ii. Telmisartan does not exhibit any partial agonist activity at the at1 receptor. Telmisartan selectively binds the at1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including at2 and other less characterised at receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin ii, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (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 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 SBP. In this respect data concerning DBP are inconsistent. In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan has been compared to antihypertensive drugs such as amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, lisinopril , ramipril and valsartan.
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.
Telmisartan treatment has been shown in clinical trials to be associated with statistically significant reductions in Left Ventricular Mass and Left Ventricular Mass Index in patients with hypertension and Left Ventricular Hypertrophy.
Telmisartan treatment has been shown in clinical trials (including comparators like losartan, ramipril and valsartan) to be associated with statistically significant reductions in proteinuria (including microalbuminuria and macroalbuminuria) in patients with hypertension and diabetic nephropathy.
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.

Reduction of cardiovascular morbidity
Support for use to reduce the risk of cardiovascular events was obtained in a pair of studies. Both enrolled subjects age ≥55 years, at high cardiovascular risk as evidenced by coronary artery disease (75%), diabetes mellitus (27%) accompanied with end-organ damage (e.g., retinopathy, left ventricular hypertrophy, and, in ONTARGET only, macro- or microalbuminuria), stroke (16%), peripheral vascular disease (13%), or transient ischemic attack (4%). Patients without a history of intolerance to ACE inhibitors entered ONTARGET, and those with such a history, usually cough (90%), entered TRANSCEND, but patients with >1+ proteinuria on dipstick were excluded from TRANSCEND. For both ONTARGET and TRANSCEND trials, the primary 4-component composite endpoint was death from cardiovascular causes, myocardial infarction, stroke, and hospitalization for heart failure. The secondary 3-component composite endpoint was death from cardiovascular causes, myocardial infarction, and stroke.
ONTARGET was a randomized, active-controlled, multinational, double-blind study in 25,620 patients who were randomized to telmisartan 80 mg, ramipril 10 mg, or their combination. The population studied was 73% male, 74% Caucasian, 14% Asian, and 57% were 65 years of age or older. Baseline therapy included acetylsalicylic acid (76%), lipid lowering agents (64%), beta-blockers (57%), calcium channel blockers (34%), nitrates (29%), and diuretics (28%). The mean duration of follow up was about 4 years and 6 months. During the study, 22.0% (n=1878) of telmisartan patients discontinued the active treatment, compared to 24.4% (n=2095) of ramipril patients and 25.3% (n=2152) of telmisartan/ramipril patients.
TRANSCEND randomized patients to telmisartan 80 mg (n=2954) or placebo (n=2972). The mean duration of follow up was 4 years and 8 months. The population studied was 57% male, 62% Caucasian, 21% Asian, and 60% were 65 years of age or older. Baseline therapy included acetylsalicylic acid (75%), lipid lowering agents (58%), beta-blockers (58%), calcium channel blockers (41%), nitrates (34%) and diuretics (33%). During the study, 17.7% (n=523) of telmisartan patients discontinued the active treatment, compared to 19.4% (n=576) of placebo patients.
The results for the TRANSCEND trial are summarized in Table 1, and the results for ONTARGET are summarized in Table 2, below:

Table 1 Incidence of the Primary and Secondary Outcomes from TRANSCEND

	Telmisartan vs. Placebo (n=2954) (n=2972)		
	No. of Events Telmisartan / Placebo	**Hazard Ratio 95% CI**	**p-value**
*Composite of CV death, myocardial infarction,stroke, or hospitalization for heart failure	465 (15.7%) / 504 (17.0%)	0.92 (0.81 – 1.05)	0.2129
*Composite of CV death, myocardial infarction, or stroke	384 (13.0%) / 440 (14.8%)	0.87 (0.76 – 1.00)	0.0483
Individual components of the primary composite endpoint	No. of Events Telmisartan / Placebo	Hazard Ratio 95% CI	p-value
**All non-fatal MI	114 (3.9%) / 145 (4.9%)	0.79 (0.62 – 1.01)	0.0574
** All non-fatal strokes	112 (3.8%) / 136 (4.6%)	0.83 (0.64 – 1.06)	0.1365

* The primary endpoint was defined as the time to first event. In case of multiple simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with composite (primary or secondary) outcomes.
** For individual components of the primary composite endpoints, all events, regardless whether or not they were the first event, were considered. Therefore, they are more than the first events considered for the primary or secondary composite endpoint.

Table 2: Incidence of the Primary and Secondary Outcomes from ONTARGET

	Telmisartan vs. Ramipril (n=8542) (n=8576)	
	No. of Events Telmisartan / Ramipril	**Hazard Ratio 97.5% CI**
Composite of CV death, myocardial infarction, stroke, or hospitalization for heart failure	1423 (16.7%) / 1412 (16.5%)	1.01 (0.93 – 1.10)
Composite of CV death, myocardial infarction, or stroke	1190 (13.9%) / 1210 (14.1%)	0.99 (0.90 – 1.08)

Although the event rates in ONTARGET were similar on telmisartan and ramipril, the results did not unequivocally rule out that Telmisartan may not preserve a meaningful fraction of the effect of ramipril in reducing cardiovascular events. However, the results of both ONTARGET and TRANSCEND do adequately support Telmisartan being more effective than placebo would be in this setting, particularly for the end point of time to cardiovascular death, myocardial infarction, or stroke.
In ONTARGET, there was no evidence that combining ramipril and Telmisartan reduced the risk of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure greater than ramipril alone; instead, patients who received the combination of ramipril and telmisartan in ONTARGET experienced an increased incidence of clinically important renal dysfunction (e.g., acute renal failure) compared to patients receiving Telmisartan or ramipril alone.
Multiple sub-group analyses did not demonstrate any differences in the 4-component composite primary endpoint based on age, gender, or ethnicity for either ONTARGET or TRANSCEND trial.

5.2 PHARMACOKINETIC PROPERTIES
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) 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. The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. Gender differences in plasma concentrations were observed, Cmax and AUC being approximately 3-and 2-fold higher, respectively, in females compared to males without relevant influence on efficacy.
Telmisartan is largely bound to plasma protein (> 99.5 %), mainly albumin and alpha-1 acid glycoprotein. the mean steady state apparent volume of distribution (vss) is approximately 500 l. telmisartan is metabolised by conjugation to the glucuronide of the parent compound. no pharmacological activity has been shown for the conjugate. 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, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. there is no evidence of clinically relevant accumulation of telmisartan. after oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, exclusively as unchanged compound. cumulative urinary excretion is < 2% of dose. total plasma clearance (CLtot) is high (approximately 900 ml/min compared with hepatic blood flow (about 1500 ml/min).

Elderly patients
The pharmacokinetics of telmisartan do not differ between younger and elderly patients.

Patients with renal impairment
Lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Patients with 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 off springs 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
Maglumine, povidone, Sodium Hydroxide, Silica Colloidal Anhydrous, Mannitol, Sodium Stearyl Fumarate.

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
Please refer outer package for expiry date.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store at or below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister of 3x10's Count.

Packing material details:

Triple laminated Cold form (Alu - Alu) blister pack:

Blister pack comprises of triple laminated cold formable film consisting of 25µ Polyamide/45µ Aluminium foil/60µ PVC film as the forming material and plain 25µ Aluminium foil with 7gsm heat seal lacquer coating as the lidding material.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
Telmisartan should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

AUROBINDO

Aurobindo Pharma Ltd., Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad-500 038, Telangana State, India.

MANUFACTURED BY:
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Survey No's. 411/P, 425/P, 434/P, 435/P & 458/P, Green Industrial Park, Polepally Village, Jedcherla Mandal, Mahaboobnagar District, Telangana State, INDIA.

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