**USE IN PREGNANCY**
**When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.** When pregnancy is detected, telmisartan tablets should be discontinued as soon as possible.
**See WARNINGS: Fetal/Neonatal Morbidity and Mortality**

## 1. NAME OF THE MEDICINAL PRODUCT
Telmisartan Sandoz Tablets 40 mg
Telmisartan Sandoz Tablets 80 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Telmisartan Sandoz Tablets 40 mg
Each tablet contains 40 mg telmisartan.
Telmisartan Sandoz Tablets 80 mg
Each tablet contains 80 mg telmisartan.

*For a full list of excipients, see section 6.1.*

## 3. PHARMACEUTICAL FORM
Tablet.
Telmisartan Sandoz Tablets 40 mg
White, oblong, plain tablet, scored on one side and debossed with '40' on the other side.
Telmisartan Sandoz Tablets 80 mg
White, oblong, plain tablet, scored on one side and debossed with '80' on the other side.

The tablet can be divided into equal halves.

## 4. CLINICAL PARTICULARS
### 4.1 Therapeutic indications
Treatment of essential hypertension in adults.
Reduction of the risk of non-fatal stroke or non-fatal myocardial infarction in adults 55 years or older at high risk of developing major cardiovascular events who cannot tolerate an angiotensin converting 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
**Dosage**
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. 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. Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide or calcium-channel-blockers such as amlodipine, which has been shown to have an additive blood pressure lowering effect with telmisartan.

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

***Special populations***
Geriatric patients
No dose adjustment is necessary for geriatric patients.

Paediatric patients
The safety and efficacy of telmisartan for use in patients aged below 18 years have not been established

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

Hepatic impairment
In patients with mild to moderate hepatic impairment, telmisartan should be administered with caution. For telmisartan, the posology should not exceed 40 mg once daily (see section 4.3).

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

**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.
- Lactation.
- 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/1.73m$^2$).

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to "list of excipients") the use of the product is contraindicated.

**4.4 Special warnings and precautions for use**
Pregnancy
Angiotensin II receptor blockers should not be initiated during pregnancy.
Unless continued angiotensin II receptor blocker 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 blocker should be stopped immediately, and if appropriate, alternative therapy should be started.

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.

Volume and/or sodium-depleted patients
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions, especially volume and/or sodium depletion, should be corrected before the administration of 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. Telmisartan should be used with caution in these patients.

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 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 transplant.
Telmisartan is not removed from blood by hemofiltration and is not dialyzable.

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 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.

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 telmisartan.

Ethnic differences
As observed for angiotensin converting enzyme inhibitors, angiotensin receptor blockers including telmisartan 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.

Ischaemic heart disease
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.

**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, telmisartan 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 not 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 hyperkalaemia. 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 telmisartan 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 15 mg/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**
Telmisartan may increase the hypotensive effect of other antihypertensive agents.

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 blockers including telmisartan. 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 telmisartan should be adequately hydrated and their renal function should be monitored 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).

**Clinical Laboratory Findings**
In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.
*Hemoglobin:* A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.
*Creatinine:* A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.
*Liver Enzymes:* Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

**4.6 Fertility, pregnancy and lactation**
Pregnancy
The use of angiotensin II receptor blockers 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 blocker should be stopped immediately, and, if appropriate, alternative therapy should be started. Unless continued angiotensin II receptor blocker 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.

Non-clinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

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

Angiotensin II receptor blockers 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).

Should exposure to angiotensin II receptor blocker 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
Telmisartan 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 non-clinical studies, no effects of telmisartan on male and female fertility were observed.

**4.7 Effects on ability to drive and use machines**
No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it should be taken into account that syncope or vertigo may occasionally occur when taking antihypertensive therapy.

**4.8 Undesirable effects**
Summary of the safety profile
In patients treated for hypertension , the overall incidence of adverse events reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in controlled trials. 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 telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

Tabulated summary of adverse reactions
The following adverse drug reactions derived from the use of telmisartan as monotherapy in clinical trials in patients treated for hypertension or from post-marketing experience, are shown in the table below classified by MedDRA System organ class and MedDRA Preferred terms. The listing also takes into account serious adverse events and adverse events 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.

| **MedDRA System Organ Class** | **Adverse reactions** |
|---|---|
| Infections and infestations | sepsis (including fatal outcome) |
| | upper respiratory tract infection |
| | urinary tract infection (including cystitis) |

| | |
|---|---|
| | cystitis |
| Blood and lymphatic system disorders | thrombocytopenia |
| | anaemia |
| | eosinophilia |
| Immune system disorders | anaphylactic reaction |
| | hypersensitivity |
| Metabolism and nutrition disorders | hyperkalaemia |
| | hypoglycaemia (in diabetic patients) |
| | hyponatraemia |
| Psychiatric disorders | depression |
| | anxiety |
| | insomnia |
| Nervous system disorders | syncope (faint) |
| Eye disorders | Visual impairment |
| Ear and labyrinth disorders | vertigo |
| Cardiac disorders | bradycardia |
| | tachycardia |
| Vascular disorders | hypotension |
| | orthostatic hypotension |
| Respiratory, thoracic and mediastinal disorders | dyspnoea |
| Gastrointestinal disorders | abdominal pain |
| | diarrhoea |
| | vomiting |
| | dyspepsia |
| | dry mouth |
| | flatulence |
| | abdominal discomfort |
| Hepatobiliary disorders | hepatic function abnormal / liver disorder<br>*Most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions.* |
| Skin and subcutaneous tissue disorders | angioedema (including fatal outcome) |
| | drug eruption |
| | toxic skin eruption |
| | urticaria |
| | eczema |

| | |
|---|---|
| | erythema |
| | rash |
| | pruritus |
| | hyperhidrosis |
| Musculoskeletal, connective tissue disorders | arthralgia |
| | back pain |
| | pain in extremity (leg pain) |
| | tendon pain (tendonitis like symptoms) |
| | muscle spasms (cramps in legs) |
| | myalgia |
| Renal and urinary tract disorders | renal impairment including acute kidney injury |
| General disorders and administration site conditions | chest pain |
| | asthenia (weakness) |
| | influenza like illness |
| Investigations | hepatic enzyme increased |
| | blood creatinine increased |
| | blood creatine phosphokinase increased |
| | haemoglobin decreased |
| | blood uric acid increased |

**4.9 Overdose**
Limited information is available with regard to overdose in humans.

Symptoms
The most prominent manifestations of telmisartan overdose were hypotension, tachycardia, bradycardia also occurred.

Therapy
If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by haemo filtration and is not dialyzable .

## 5. PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Angiotensin II receptor blocker, ATC Code: C09CA07.

Mode of action
Telmisartan is an orally active and specific angiotensin II receptor (type AT1) blocker. 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 man, 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.

Pharmacodynamics
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 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 antihypertensive efficacy of telmisartan has been compared to agents representative of other classes of antihypertensive drugs (in clinical trials comparing telmisartan to agents 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.

Clinical Trials
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

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.

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 (Vss) 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.

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 ($CL_{tot}$) is high (approximately 900 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Linearity

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.

***Special Populations***

Gender differences

Gender differences in plasma concentrations were observed, $C_{max}$ and AUC being approximately 3-and 2- fold higher, respectively, in females compared to males without relevant influence on efficacy.

Geriatric patients

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

Renal impairment

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium Hydroxide
Meglumine
Povidone K25
Lactose monohydrate
Povidone K30
Crospovidone
Lactose anhydrous
Magnesium Stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Please refer to outer carton.

### 6.4 Special precautions for storage

Store below 30°C. Keep out of the reach and sight of children. Store in the original package in order to protect from moisture.

### 6.5 Nature and contents of container

Al/Al blisters containing 7, 10, 14, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets.
*Not all pack sizes may be marketed.*

### 6.6 Special precautions for disposal

No special requirements.

## 7. MANUFACTURER

Lek Pharmaceuticals d.d.
Verovškova 57
1526 Ljubljana
Slovenia

Or

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## 8. DATE OF REVISION OF THE TEXT

Feb 2023