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INSTRUCTION
for medical use

HYPOTEL®

Composition:
active substances: telmisartan;
1 tablet contains telmisartan 40 mg or 80 mg;
excipients: sodium hydroxide, meglumine, mannitol (E 421), crospovidone, magnesium stearate.

Pharmaceutical form. Tablets.
Main physicochemical properties: white or almost white, round biconvex tablets.

Pharmacotherapeutic group. Simple preparations of angiotensin II antagonists.
ATC code C09C A07.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action.
Telmisartan is a specific and effective angiotensin II receptor antagonist (type AT_1). Telmisartan with very high affinity replaces angiotensin II in the places of its binding with AT_1-type receptors which are responsible for the activity of angiotensin II. Telmisartan does not exhibit any partial agonist effect on the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less studied 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 does not 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, 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The blocking effect is maintained over 24 hours and still measurable up to 48 hours.
Pharmacokinetics.
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) to approximately 19% (160 mg). In 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food.
Linearity/non-linearity. It is believed that a slight reduction in AUC does not lead to a reduction in therapeutic efficacy. There is no linear relationship between dose and plasma level. The maximum plasma concentration (C_{max}) and, to a lesser extent, AUC is increased disproportionately at doses more than 40 mg.
Distribution. Telmisartan is largely bound to plasma protein (> 99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean volume of distribution (V_{ss}) is approximately 500 L.

Metabolism. Telmisartan is metabolized by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.
Elimination. Telmisartan is characterized by biexponential pharmacokinetics with a terminal elimination half-life of >20 hours. C_{max} and, to a smaller extent AUC increase disproportionately with dose. There is no data 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 administration, telmisartan is nearly exclusively excreted with the feces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1.000 ml/min) compared with hepatic blood flow (about 1.500 ml/min).
Special populations.
Children. The results of pharmacokinetic studies in children generally correspond to data obtained for adults, and confirm the nonlinearity of telmisartan in particular for C_{max}.
Gender. Plasma concentrations were observed, with C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.
Elderly patients. The pharmacokinetics of telmisartan are not different in elderly patients (aged 65 years) compared with younger patients.
Patients with renal impairment. Patients with moderate to moderate and severe renal insufficiency increasing of 2-fold 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.
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.

Clinical characteristics.
Indications.
Hypertension.
Treatment of essential hypertension in adults.
Prevention of cardiovascular diseases.
Reduction of the incidence of cardiovascular disease in patients with:
- manifest atherothrombotic cardiovascular disease (ischemic heart disease, stroke or history of peripheral arterial disease);
- II type of diabetes mellitus with documented damage of target organs.

Contraindications.
- hypersensitivity to drug components;
- pregnant women or women planning to get pregnant (see sections (Administration details», «Use during pregnancy or breast feeding»);
- obstructive biliary disorders;
- severely impaired liver function;
- children's age (less than 18 years).

Concomitant use of telmisartan and aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) is contraindicated (see sections «Pharmacological properties» and «Interaction with other medicinal products and other forms of interaction»).

Interaction with other medicinal products and other forms of interaction.
Digoxin.
Concomitant administration of telmisartan and digoxin increases average peak plasma concentrations of digoxin (by 49%) and minimal concentrations (by 20%). Monitoring of digoxin levels is useful on the early stages of treatment in case of dose adjustment and discontinuation of telmisartan, for maintaining them within therapeutic range.

As other drugs inhibiting renin-angiotensin system, telmisartan may provoke hyperkalemia (see Section «Peculiarities of use»). The risk may increase in case of treatment in combination with other agents which may cause hyperkalemia (potassium-containing salt substitutes, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs, including COX-2 selective inhibitors), heparin, immune-suppressors (cyclosporine or tacrolimus) and trimethoprim).

The occurrence of hyperkalemia depends on the corresponding risk factors. The risk increases in case of using the above mentioned therapeutic combinations. Especially high is the risk when using a combination with potassium-sparing diuretics and potassium-containing salt substitutes. Combination with ACE or nonsteroidal anti-inflammatory drugs is less risky on condition of strict compliance with the precautions in use.

Concomitant administration is not recommended.

Potassium-sparing diuretics or potassium supplements. Such angiotensin II receptor antagonists as telmisartan lessen the loss of potassium caused by diuretics. Potassium-sparing diuretics, such as spironolactone, eplerenone, triamterene, or amiloride, potassium-containing additives and potassium-containing salt substitutes, may significantly increase serum potassium concentration. If the concomitant use is indicated because of documented hypokalemia, the drugs should be taken with caution frequently controlling serum potassium level.

Lithium. Cases of reversible increase in serum lithium concentration and increased toxicity during concomitant intake of lithium with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists II, including telmisartan, are known. If it is necessary to prescribe this combination, serum lithium level should be thoroughly controlled during concomitant use.

Concomitant administration requires caution.

Nonsteroidal anti-inflammatory drugs. NSAIDs (i.e. acetylsalicylic acid in anti-inflammatory treatment doses, COX-2 inhibitors and non-selective NSAIDs) may reduce antihypertensive effect of angiotensin II receptor antagonists.

In some patients with renal function impairment (for instance, in patients with dehydration or elderly patients with deterioration of renal function) combined use of angiotensin II receptor antagonists and cyclooxygenase-inhibiting agents may lead to further deterioration of renal function, including possible acute renal failure, which is reversible as a rule. Therefore, this combination should be prescribed with caution, especially in elderly patients. Patients should be provided with adequate hydration; Besides, after starting the combined therapy, as well as from time to time in future, renal function should be controlled.

There are data that a combined treatment with telmisartan and ramipril increases AUC_{0-24} and C_{max} of ramipril and ramiprilate by 2.5-fold. The clinical significance of this observation is unknown.

Diuretics (thiazide or loop diuretics). Prior treatment with high doses of diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (a thiazide diuretic) may result in loss of volume and the risk of arterial hypotension if treatment with telmisartan is initiated.

Should be kept in mind when concomitant treatment.

Other antihypertensive agents. The ability of telmisartan to reduce blood pressure may be increased by concomitant use of other antihypertensive agents.

Clinical data have shown that double blockade of renin-angiotensin-aldosterone system (RAAS) by combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher incidence of such adverse effects as arterial hypotension, hyperkalemia and reduced renal function (including acute renal failure) compared to the use of one RAAS-active agent (see sections «Pharmacodynamics», «Contraindications» and «Administration details»).

On the basis of pharmacological properties of baclofen and amifostine, it may be expected that these medicinal products may increase the antihypertensive effect of all antihypertensive agents, including telmisartan. Furthermore, orthostatic hypotension may be induced by alcohol, barbiturates, narcotics and antidepressants.

Corticosteroids (systemic use). Reduction of antihypertensive effect.

Administration details.

Pregnancy. During pregnancy, treatment with angiotensin II receptor antagonists can not be started. If prolongation of therapy with angiotensin II receptor antagonists is not considered absolutely necessary for the patient planning to conceive, she should start alternative antihypertensive therapy with a determined safety profile for use during pregnancy. If pregnancy is detected, treatment with angiotensin II antagonists should be stopped immediately an alternative treatment should be started if necessary (see sections «Contraindications» and «Use during pregnancy or breast feeding»).
Hepatic failure. Hypotel should not be prescribed for patients with cholestasis, obstructive diseases of bile ducts and severe hepatic failure (see Section "Contraindications") as telmisartan is excreted mainly with bile. A decrease of hepatic clearance of telmisartan may be anticipated in such patients.
Caution should be exercised when prescribing Hypotel for patients with mild to moderate hepatic failure.
Renovascular hypertension. There is an increased risk of severe arterial hypotension and renal failure, if patients with bilateral renal artery stenosis or stenosis in a solitary functioning kidney are treated with drugs affecting RAAS.
Renal failure and kidney transplantation. When Hypotel is prescribed for patients with impaired renal function, it is recommended to monitor the serum levels of potassium and creatinine from time to time. There is no experience of using telmisartan in patients with resent kidney transplantation.
Decreased intravascular fluid volume. Symptomatic hypotension, especially after the first dose of Hypotel, may occur in patients with decreased intravascular volume and/or sodium level, which occurs as a result of treatment with diuretics, limiting the amount of salt coming with food, diarrhea or vomiting. Such conditions especially decreased intravascular volume and/or sodium level, should be corrected before using Hypotel.
Dual blockade of the renin-angiotensin-aldosterone system.
There is evidence that concomitant use of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and reduces renal function (including acute renal failure).
Therefore, double blockade by combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is not recommended (see sections «Pharmacodynamics» and «Interaction with other medicinal products and other forms of interaction»).
If double blockade is considered absolutely necessary, it has to be conducted only under medical supervision and on condition of constant 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 requiring stimulation of the renin-angiotensin-aldosterone system.
In patients whose vascular tone and renal function depend mainly on renin-angiotensin-aldosterone system activity (for instance, in patients with severe congestive heart failure or apparent kidney disease, including renal artery stenosis) using telmisartan with other medical preparations affecting the renin-angiotensin-aldosterone system may cause acute arterial hypotension, hyperazotemia, oliguria, occasionally – acute renal failure (see Section «Adverse reactions»).
Primary hyperaldosteronism. Patients with primary hyperaldosteronism in general do not react to antihypertensive preparations which act by blocking the renin-angiotensin system. Therefore, it is not recommended to administer telmisartan to such patients.
Stenosis of aorta and mitral valve, obstructive hypertrophic cardiomyopathy. As with other vasodilators, special caution should be exercised when prescribing the drug for patients diagnosed with stenosis of aorta, mitral valve or obstructive hypertrophic cardiomyopathy.
Diabetic patients taking insulin or antidiabetic drugs. During treatment with telmisartan such patients may develop hypokalemia. The necessity of appropriate blood glucose level control should be regarded in such patients. If indicated, insulin or antidiabetic drug dose adjustment may be required.
In diabetic patients with cardiovascular risks (diabetic patients with concomitant coronary artery disease) the risk of lethal myocardial infarction and sudden cardiovascular death may be higher in case of treatment with antihypertensive drugs such as angiotensin II receptor antagonists and ACE inhibitors. In diabetic patients the course of concomitant coronary artery diseases may be

asymptomatic, and therefore they may be undiagnosed. Diabetic patients should be thoroughly examined, for instance, by stress test to detect and treat concomitant coronary artery diseases before prescribing the drug.
Hyperkalemia. During the whole period of using medical preparations which affect renin-angiotensin-aldosterone system, hyperkalemia may occur.
In elderly patients, patients with renal failure, diabetes, in patients concomitantly using other medical preparations which may increase potassium levels, and/or patients with concomitant diseases, hyperkalemia may cause lethal outcome.
Before concomitant prescription of medical preparations which suppress renin-angiotensin system, it is necessary to evaluate the risks and benefits ratio.
The main risk factors of hyperkalemia which require attention:
- Diabetes mellitus, renal failure, age (over 70 years).
- Combined therapy with one or several drugs, which affect renin-angiotensin system, and/or potassium additives. Preparations or therapeutic groups which may provoke hyperkalemia, include potassium-containing salt substitutes, potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, NSAIDs, including COX-2 selective inhibitors, heparin, immunosuppressors (cyclosporine or tacrolimus) and trimethoprim.
- Concomitant diseases, especially dehydration, acute cardiac decompensation, metabolic acidosis, impairment of renal function, rapid deterioration of kidney condition (e.g. infectious diseases), cell lysis (e.g. acute limb ischemia, acute necrosis of skeletal muscles, major trauma).

Patients at risk should be carefully monitored for serum potassium concentrations (see Section «Interaction with other medicinal products and other forms of interaction»).
Ethnic differences. As all other angiotensin II receptor antagonists, telmisartan is apparently less effective in lowering blood pressure in black race patients than in representatives of other races. This might be explained by high prevalence of low renin conditions in black race patients with arterial hypertension.
Others. As with any other antihypertensive drug, a significant blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease may lead to myocardial infarction or stroke.

Use during pregnancy or lactation.
Pregnancy.
The medicinal product is contraindicated in pregnant women or women planning to conceive. If during treatment with this product pregnancy is confirmed, its use must be stopped immediately and, if necessary, replaced by another medicinal agent permitted for use in pregnant women (see sections «Contraindications» and «Administration details»).
There are no appropriate data on the use of telmisartan in pregnant women.
Epidemiological justification of the risk of teratogenicity due to the use of ACE inhibitors during the first trimester of pregnancy was not convincing, however, a slight increase in the risk may not be excluded. Though there are no controlled epidemiological data on the risk of teratogenicity when using angiotensin II receptor antagonists, such risks may exist for this class of medicinal products. When planning pregnancy, the drug should be replaced in advance with another antihypertensive product with a determined safety profile for use during pregnancy. If pregnancy is detected, treatment with angiotensin II antagonists should be stopped immediately an alternative treatment should be started if necessary.
The use of angiotensin II receptor antagonists during the II and III trimesters of pregnancy causes foetotoxicity in humans (violation of renal function, oligohydramnios, delayed skull bone formation) and neonatal toxicity (hepatic failure, hypotony, hyperkalemia). If the use of angiotensin II receptor antagonists was started from the second trimester of pregnancy, it is recommended to conduct an ultrasonic examination of renal function and skull bones of the fetus. The condition of the infants whose mothers took angiotensin II receptor antagonists should be closely monitored for the presence of arterial hypotension (see sections «Contraindications» and «Administration details»).

Breast feeding.

Due to the lack of information on the use of telmisartan during breastfeeding, Hypotel is not recommended for use. Advantage is given to alternative treatment with a better studied safety profile, especially when breastfeeding a newborn or premature baby.

Fertility.

In the course of preclinical studies, no effect of telmisartan on fertility of men and women was detected.

Effect on reaction rate when driving motor transport or operating other mechanisms.

When driving motor transport or operating other mechanisms it should be taken into account that dizziness or hypersomnia may occur when taking antihypertensive therapy, including Hypotel.

Administration and dosage.

Treatment of arterial hypertension.

The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg (use in the appropriate dosage). 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 4-8 weeks after the start of treatment.

Prevention of cardiovascular diseases.

The recommended dose is 80 mg one time per day. The efficacy of telmisartan in doses less than 80 mg for prevention of cardiovascular diseases is unknown.

At the beginning of treatment with telmisartan to prevent cardiovascular diseases, it is recommended to monitor blood pressure, and if necessary, adjust the doses of the drugs which decrease the blood pressure.

Special groups of patients.

Kidney dysfunction. Experience of treatment of patients with kidney failure or patients on hemodialysis is limited. Such patients are recommended to start treatment with the low dose of 20 mg (use in the appropriate dosage). For patients with mild to moderate renal insufficiency dose adjustment is not required.

Concomitant use of telmisartan and aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) is contraindicated (see Section «Contraindications»).

Liver dysfunction. Hypotel is contraindicated for patients with severe liver dysfunction.

For patients with mild to moderate liver disorders the daily dose should not be more than 40 mg 1 time per day (see Section "Peculiarities of use").

Elderly. No dose adjustment is required for elderly patients.

Administration.

Hypotel should be taken orally once daily with plenty of liquid, with/or without food.

Tablets should be stored in the sealed blister to protect from humidity. Tablets should be removed from the blister immediately before use.

Children.

Safety and efficacy of the drug Hypotel in children (aged less than 18 years) has not been studied.

Overdose.

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

Symptoms. The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Treatment. Telmisartan is not removed by hemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Treatment depends on the time since drug use and the severity of the symptoms. Recommended measures include inducing vomiting and/or gastric

lavage. Activated charcoal may be useful in the treatment of overdose. The level of electrolytes and creatinine in serum should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

Adverse reactions.
Infections and invasions: upper respiratory tract infections, including pharyngitis and sinusitis; urinary tract infections, including cystitis; sepsis, including with lethal outcome.
Blood and lymphatic system: anaemia, thrombocytopenia, eosinophilia.
Immune system: hypersensitivity, anaphylactic reaction.
Metabolism disorders: hyperkalemia, hypoglycemia (in diabetic patients).
Mental disorders: depression, insomnia, anxiety.
Nervous system: syncope, drowsiness.
Visual organs: visual impairment.
Organs of hearing and vestibular system: vertigo.
Cardiac disorders: bradycardia, tachycardia.
Vascular disorders: arterial hypotension, orthostatic hypotension.
Respiratory, thoracic and mediastinal disorders: dyspnea, cough, interstitial lung disease.
Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, meteorism, vomiting, stomach discomfort, dry mouth, dysgeusia.
Hepatobiliary system disorders: abnormal liver function/liver disorder.
Skin and subcutaneous covering: increased sweating, itching, rash, erythema, angioneurotic edema (including lethal outcome), drug-induced dermatitis, toxic dermatitis, eczema, urticaria.
Musculoskeletal system and connective tissue: myalgia, back pain (e.g. ischias), muscle spasms, arthralgia, pain in extremities, tendon pain (tendinitis-like symptoms).
Urinary system: impaired renal function, including acute renal failure.
General disorders: chest pain, asthenia (weakness), flu-like symptoms.
Laboratory data: blood creatinine increase, blood urea increase, liver enzymes increase, increase in creatine phosphokinase (CPK) levels, hemoglobin decrease.

Shelf-life.
3 years.

Storage conditions.
Store at temperatures below 25ºC in the original package.
Keep out of reach of children.

Package.
There are 10 tablets in a blister; there are 3 blisters in a carton pack.
There are 14 tablets in a blister; there are 2 or 4, or 6 blisters in a carton pack.

Conditions of supply.
On prescription.

Manufacturer.
LLC “KUSUM PHARM”.

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40020, Ukraine, Sumy oblast, Sumy, Skryabina St., 54.

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