For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Telmisartan Tablets USP 20mg/40mg/80mg

MACSART 20/40/80

COMPOSITION
Each uncoated tablet contains:
Telmisartan USP 20mg/40mg/80mg

DESCRIPTION
Telmisartan is a non-peptide angiotensin II receptor (type AT1) antagonist. It is chemically described as 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1Hbenzi midazol]-1'-yl)methyl][1,1'-biphenyl]-2 carboxylic acid. Its empirical formula is $C_{33}H_{30}N_6O_2$, its molecular weight is 514.63.

PHARMACOLOGICAL CLASSIFICATION
AngiotensinII receptor (type AT1) antagonist

PHARMACOLOGICAL ACTION:
Pharmacodynamics
Mechanism of Action:
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascularsmooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.
There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (> 3,000 fold) for the AT1 receptor than for the AT2 receptor.
Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisa- rtan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.
Pharmacokinetics
Absorption
Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan is nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.
Distribution
Telmisartan is highly bound to plasma proteins (> 99.5%), mainly albuminand α1 -acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.
Metabolism
Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.
Elimination
Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (> 97%) was eliminated unchanged in feces via biliaryexcretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). Total plasma clearance of telmisartan is > 800 mL/min. Terminal half-life and total clearance appears to be independent of dose.

INDICATIONS AND USAGE
Hypertension
Telmisartan is indicated for the treatment of hypertension, to lower blood pressure.
Cardiovascular Risk Reduction
It is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors.

DOSAGE
Hypertension
Dosage must be individualized.
The usual starting dose of Telmisartan tablets is 40 mg once a day. Blood pressure response is dose-related over the range of 20 to 80 mg.
Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. When additional blood pressure reduction beyond that achieved with 80 mg Telmisartan is required, a diuretic may be added.
No initial dosage adjustment is necessary for elderly patients or patients with renal impairment, including those on hemodialysis. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored. Telmisartan tablets may be administered with other antihypertensive agents. Telmisartan tablets may be administered with or without food.
Cardiovascular Risk Reduction
The recommended dose of Telmisartan tablets is 80 mg once a day and can be administered with or without food. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing the risk of cardiovascular morbidity and mortality. When initiating Telmisartan therapy for cardiovascular risk reduction, monitoring of blood pressure is recommended, and if appropriate, adjustment of medications that lower blood pressure may be necessary.

CONTRAINDICATIONS
It is contraindicated in patients with known hypersensitivity (e.g.anaphylaxis or angioedema) to telmisartan or any other component of this product. Do not co-administer aliskiren with telmisartan in patients with diabetes.

ADVERSE REACTION
Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations	
Uncommon:	Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis
Rare:	Sepsis including fatal outcome
Blood and the lymphatic system disorders	
Uncommon:	Anaemia
Rare:	Eosinophilia , thrombocytopenia
Immune system disorders	
Rare:	Anaphylactic reaction , hypersensitivity
Metabolism and nutrition disorders	
Uncommon: Rare:	Hyperkalaemia Hypoglycaemia (in diabetic patients)
Psychiatric disorders	
Uncommon:	Insomnia, depression
Rare:	Anxiety
Nervous system disorders	
Uncommon:	Syncope
Rare:	Somnolence
Eye disorders	
Rare:	Visual disturbance
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Bradycardia
Rare:	Tachycardia
Vascular disorders	
Uncommon:	Hypotension[4], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough
Very rare:	Interstitial lung disease
Gastrointestinal disorders	
Uncommon: Rare:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting Dry mouth, stomach discomfort, dysgeusia
Hepatobiliary disorders	
Rare:	Hepatic function abnormal/liver disorder

Skin and subcutaneous tissue disorders	
Uncommon: Rare:	Pruritus, hyperhidrosis, rash Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Muscoloskeletal and connective tissue disorders	
Uncommon: Rare:	Back pain (e.g. sciatica), muscle spasms, myalgia Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)
Renal and urinary disorders	
Uncommon:	Renal impairment including acute renal failure
General disorders and administration site conditions	
Uncommon: Rare:	Chest pain, asthenia (weakness) Influenza-like illness
Investigations	
Uncommon:	Blood creatinine increased
Rare:	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

DRUG INTERACTIONS

Aliskiren: Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid use of aliskiren with Telmisartan in patients with renal impairment (GFR < 60 mL/min).

Digoxin: When Telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

Lithium: Reversible increases in serum lithiumconcentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including TELMISARTAN. Therefore, monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selectiveCOX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3-and 2.1-fold, respectively, and Cmax and AUC of ramiprilat 2.4-and 1.5-fold, respectively. In contrast, Cmax and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Concomitant use of Telmisartan and ramipril is not recommended.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, warfarin, simvastatin, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

WARNINGS & PRECAUTIONS

Hypotension

In patients with an activated renin-angiotensin system, such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Hyperkalemia

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Impaired Hepatic Function

As the majority of telmisartan is eliminated by biliaryexcretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin- aldosteronesystem, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan.

In studies of ACE inhibitors in patients with unilateralor bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on Telmisartan and other agents that affect the RAS.

Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR < 60 mL/min/1.73 m²).

PREGNANCY:

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Telmisartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Telmisartan for hypotension, oliguria, and hyperkalemia.

Lactation:

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Carcinogenesis, Mutagenesis and Fertility Impairment

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m²basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan > 100 times and > 25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m²basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with telmisartan tablets would behypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

STORAGE

Store below 30°C in a dry place. Protect from light.
Keep out of reach of children.

PRESENTATION

Blister pack of 10 tablets.

MACLEODS

Manufactured in India by:
MACLEODS PHARMACEUTICALS LTD.
Off, Atlanta Arcade, Marol Church Road,
Andheri (E), Mumbai - 400 059.