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

℞ Cilnidipine & Telmisartan Tablets 20 mg + 40 mg

CILACAR® T 20/40

GENERIC NAME
Cilnidipine and Telmisartan Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Composition:
Each film coated tablet contains:
Cilnidipine IP ..... 20 mg
Telmisartan IP ..... 40 mg
Colours: Ferric Oxide USP - NF (Red) & Titanium Dioxide IP

DOSAGE FORM AND STRENGTH
Film Coated Tablets

CLINICAL PARTICULARS
Therapeutic indication
It is indicated for the treatment of essential hypertension.

Posology and method of administration
The recommended oral dosage is 1 tablet once daily or as directed by the Physician.
Method of administration: For oral use only.
Patients should be advised to swallow the tablets whole with liquid and should not be chewed or crushed. To achieve the best possible results, take your dose at the same time(s) each day.

Contraindications
Aortic stenosis, advanced.
Hypersensitivity to cilnidipine or other calcium channel antagonists.
Telmisartan 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.

Special warnings and precautions for use
Cilnidipine
Careful Administration (Cilnidipine should be administered with care in the following patients.): Patients with serious hepatic dysfunction [The plasma concentration may become elevated.] Patients with a history of serious adverse reactions to calcium antagonists.
Important Precautions:
• As it has been reported that sudden withdrawal of a calcium antagonist caused aggravation of certain symptoms. Therefore, if the discontinuation of cilnidipine is necessary, the dosage should be gradually decreased under close observation.
• If Cilnidipine is withdrawn from a daily dose of 5 mg, appropriate measures, such as replacement with other antihypertensive agents, should be taken.
• Direct the patient not to discontinue this drug without physician's instructions.
Effects on Ability to Drive and Operate Machine:
The symptoms, such as dizziness may occur because of the hypotensive action from this drug.
Give warning against engaging in hazardous activities requiring alertness, such as working at a height, operating machinery or driving motor vehicles.
Telmisartan
Fetal Toxicity
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
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 biliary excretion, 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.
Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAS)
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. The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of Telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. 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).

Drugs interactions
Cilnidipine
Cilnidipine is chiefly metabolized by the drug-metabolizing enzyme CYP3A4 and in part by CYP2C19.
Precautions for co-administration (Cilnidipine and the following drugs should be co-administered with care):
Other anti-hypertensive drugs, Digoxin, Cimetidine, Rifampicin, Antifungal azoles (Itraconazole, Miconazole etc), Grape fruit juice.
Telmisartan
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 lithium concentrations 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 selective COX-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.

Use in Special populations
Cilnidipine
Pregnancy-
Dosage should not be given to pregnant ladies or Expecting women. It is reported that on the Experiments on animals (Rats), Fetal Toxicity and postponement of pregnancy period & Delivery was observed.
Lactation-
It is advisable to avoid dosage to feeding mothers, in case of unavoidable reason, feeding to babies should be stopped. In case of Experiments on animals, it is observed that the dosage transfers to feeding milk.
Renal Impairment:
Repeated oral administration of Cilnidipine at a dose of 10 mg once a day for 7 days in patients with impaired renal function caused no differences in the pharmacokinetic profile compared with that in patients with normal renal function.
Pediatric use:
The safety of Cilnidipine in pediatric patients has not been established (no clinical experience).
Elderly patients:
Cilnidipine should be administered carefully under close observation of the patient's condition, taking such measures as starting with a lower dose (e.g. 5 mg). Use in the Elderly is generally acknowledged that the excessive hypotensive action should be avoided in the elderly.
Telmisartan
Pregnancy
Risk Summary Telmisartan can cause fetal harm when administered to a pregnant woman. 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 (see Clinical Considerations). 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. Studies in rats and rabbits with telmisartan showed fetotoxicity only at maternally toxic doses. When pregnancy is detected, discontinue Telmisartan as soon as possible. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Clinical Considerations Disease-associated maternal and/or embryo/fetal risk Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly. Fetal/Neonatal adverse reactions Use of drugs that act on the RAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. 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. In patients taking Telmisartan during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue Telmisartan, unless it is considered lifesaving for the mother. 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. If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.
Data
Animal Data 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 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m2 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/m2 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. 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/m2 basis, the maximum recommended human dose of telmisartan (80 mg/day).
Lactation
Risk Summary There is no information regarding the presence of telmisartan in human milk, the effects on the breastfed infant, or the effects on milk production. Telmisartan is present in the milk of lactating rats (see Data). Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with Telmisartan. Data Telmisartan was present in the milk of lactating rats at concentrations 1.5 to 2 times those found in plasma from 4 to 8 hours after administration.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Neonates with a history of in utero exposure to Telmisartan If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.
Geriatric Use
Of the total number of patients receiving Telmisartan in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Of the total number of patients receiving Telmisartan in the cardiovascular risk reduction study (ONTARGET), the percentage of patients ≥65 to < 75 years of age was 42%; 15% of patients were ≥75 years old. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Hepatic Insufficiency
Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency.

Effects on the Ability to Drive and Use Machines
There are no reported effects of the drug on the ability to drive or handle machinery.

Undesirable effects
Cilnidipine
(1) Clinical significant adverse reactions:
• Hepatic function disorder and jaundice accompanied with increased AST (GOT), ALT (GPT) and α-GTP may occur. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of cilnidipine, should be taken.
• Thrombocytopenia (incidence: <0.1 %): Since thrombocytopenia may occur, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of cilnidipine, should be taken.
(2) Other adverse reactions –
If any of the following adverse reactions occur, appropriate measures should be taken depending on the symptoms.

	Less than 0.1 ~ 5%	Less than 0.1%	Frequency unknown
Hepatic	Increase in AST(GOT), ALT(GPT), LDH etc	ALP increased	
Renal	Increase in Creatinine or Urea Nitrogen, Urinary Protein positive	Urine Sediment present	
Psychoneurological	Headache, Headache dull, Dizziness, Dizziness on standing up, Shoulder muscle stiffness	Sleepiness,Insomnia, Tremor finger, Amnesia	Numbness
Cardiovascular	Flushed face, Palpitation, Feeling hot, ECG abnormal (ST depressed, inverted T waves), Decrease in blood pressure	Chest pain, cardiothoracic ratio increased, tachycardia, AV block, feeling cold	Extrasystole
Gastrointestinal	Nausea, Vomiting, Abdominal pain	Constipation, bloating, thirst, gingival hypertrophy, heartburn, diarrhea	
Hypersensitivity	Rash	Redness, Itching	Photosensitivity
Hematologic	Increase or decrease in WBC, Neutrophil, Hemoglobin	Increase or decrease in RBC, Hematocrit, Eosinophil, Lymphocytes	
Other	Oedema (Face, Lower leg etc), General Malaise, pollakiuria, Increase in serum cholesterol, Increase or decrease in CK (CPK), Uric acid, Serum potassium, and Serum phosphorus	Feeling of weakness, gastrocnemius muscle cramps, periophthalmic dryness, ocular hyperemia and feeling of irritation, dysgeusia, urine sugar positive, increase or decrease in fasting blood sugar, total protein, serum Ca and CRP, cough	Tinnitus

Telmisartan
The following adverse reaction is described elsewhere in labeling:
• Renal dysfunction upon use with ramipril
Clinical Trials Experience Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. Hypertension Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy. In placebo-controlled trials involving 1041 patients treated with various doses of Telmisartan (20 to 160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo. Adverse events occurring at an incidence of ≥1% in patients treated with Telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.
Table 1 Adverse Events Occurring at an Incidence of ≥1% in Patients Treated with Telmisartan and at a Greater Rate Than Patients Treated with Placebo

	Telmisartan n=1455	Placebo n=380
	%	%
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with Telmisartan tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials. The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients. The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%). In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with Telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to Telmisartan tablets:
Autonomic Nervous System: impotence, increased sweating, flushing; Body as a Whole: allergy, fever, leg pain, malaise; Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia; Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders; Metabolic: gout, hypercholesterolemia, diabetes mellitus; Musculoskeletal: arthritis, arthralgia, leg cramps; Psychiatric: anxiety, depression, nervousness; Resistance Mechanism: infection, fungal infection, abscess, otitis media; Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis; Skin: dermatitis, rash, eczema, pruritus; Urinary: micturition frequency, cystitis; Vascular: cerebrovascular disorder; and Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.
During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).
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 because of 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 because of 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 because of abnormal hepatic function.
Cardiovascular Risk Reduction
Because common adverse reactions were well characterized in studies of telmisartan in hypertension, only adverse events leading to discontinuation and serious adverse events were recorded in subsequent studies of telmisartan for cardiovascular risk reduction. In TRANSCEND (N=5926, 4 years and 8 months of follow-up), discontinuations for adverse events were 8.4% on telmisartan and 7.6% on placebo. The only serious adverse events at least 1% more common on telmisartan than placebo were intermittent claudication (7% vs 6%) and skin ulcer (3% vs 2%).

Overdose
Cilnidipine
Overdosage of Cilnidipine may cause excessive reduction in blood pressure. If reduction in blood pressure is remarkable, appropriate measures such as lifting lower extremities, fluid therapy and administration of vasopressors should be taken. Hemodialytical removal of cilnidipine is not effective because of its high rate of protein-binding.
Telmisartan
Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with Telmisartan tablets would be hypotension, 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 hemofiltration and is not dialyzable.

PHARMACOLOGICAL PROPERTIES
Mechanism of Action
Cilnidipine
Experimental data suggest that cilnidipine binds to the dihydropyridine binding sites of the L-type voltage dependent calcium channel and inhibits Ca^{2+} influx across the cell membranes of vascular smooth muscle cells via this channel (rabbits in vitro).
Consequently, vascular smooth muscle is relaxed, causing vasodilation. Through this mechanism, cilnidipine is considered to have a hypotensive action.
Cilnidipine inhibits Ca^{2+} influx via N-type voltage dependent calcium channels in the sympathetic nerve cell membrane. The inhibition of Ca^{2+} influx via N-type voltage dependent calcium channel was observed over a similar range of drug concentrations to those inhibiting L-type voltage dependent Ca^{2+} channels (rats in vitro).
Consequently, release of norepinephrine from sympathetic nerve terminals would be inhibited. Cilnidipine is considered to suppress the reflex increase in heart rate which may be mediated by sympathetic activation after blood pressure reduction and to inhibit stress-related hypertension through this mechanism
Telmisartan
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 vascular smooth 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 telmisartan 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.

Pharmacodynamic Properties
Cilnidipine
Antihypertensive Effect: In various hypertensive animal models (spontaneously hypertensive rats, renal hypertensive rats and dogs, DOCA salt hypertensive rats, and stroke-prone spontaneously hypertensive rats, a single oral dose of cilnidipine showed a gradual and long-lasting hypotensive action that was dose-dependent at 1 mg/kg or more.
In contrast, it showed a weak hypotensive action in normotensive rats. The duration of the action was not prolonged by an excessive dosage. In renal hypertensive dogs, cilnidipine showed an additive effect when co-administered with a α-blocker or an angiotensin-converting enzyme (ACE) inhibitor.
In stroke-prone spontaneously hypertensive rats and renally hypertensive dogs, repeated oral doses of cilnidipine had a stable hypotensive action which did not show attenuation. Discontinuation of cilnidipine did not cause a rebound in blood pressure.
In conscious and unrestrained spontaneously hypertensive rats, cilnidipine did not increase the heart rate during hypotension. Cilnidipine did not increase the plasma noradrenaline level during hypotension, nor did it cause a significant decrease, which an adrenergic blocker (guanethidine sulfate) did. Cilnidipine did not cause orthostatic hypotension, although a ganglion blocker (pentolinium) did in a tilt test using rabbits.
In patients with essential hypertension, a single daily dose of cilnidipine showed an hypotensive action that maintained for 24 hours and was still evident early in the next morning. Power spectral analysis of the R-R intervals of 24 hours electrocardiogram revealed that cilnidipine did not increase sympathetic activity or the heart rate as a reflex response to the reduction of blood pressure.
Inhibitory Action on Stress-Induced Pressor Response: In conscious and unrestrained spontaneously hypertensive rats, cilnidipine inhibited the elevation of blood pressure and plasma norepinephrine levels induced by cold stress. Cilnidipine also inhibited the elevation of blood pressure induced by air jet stress (mental stress) in rats.
In healthy adult male volunteers whose blood pressure was elevated by ≥20% in cold stress test, cilnidipine suppressed the elevation of blood pressure induced by cold stress.
Inhibitory Action on Sympathetic Stimulation-Induced Pressor Response: In pithed spontaneously hypertensive rats, cilnidipine suppressed the elevation of blood pressure induced by electrical sympathetic stimulation.
In isolated and perfused mesenteric arterial vascular preparation in spontaneously hypertensive rats, cilnidipine also inhibited the release of norepinephrine induced by electrical sympathetic stimulation.
Effect on Cerebral Circulation: In spontaneously hypertensive rats, cilnidipine did not decrease cerebral blood flow even if the dose which decreases blood pressure by 30-40% in rats was administered. The auto-regulation of cerebral blood flow was satisfactorily maintained while the blood pressure was decreased.
In hypertensive patients complicated by cerebrovascular disease, the cerebral blood flow was maintained while blood pressure was lowered.
Effects on Cardiac Function: In dogs, cilnidipine decreased heart rate and myocardial contractility at a higher dose than that inducing an increased flow of arterial blood.
In anesthetized open chest dogs, cilnidipine decreased the myocardial oxygen consumption at dose inducing hypotension. At the time, it neither caused tachycardia nor affected cardiac contractility.
In patients with essential hypertension, cilnidipine did not affect heart rate while the blood pressure was decreased and in patients with abnormal cardiothoracic ratio (CTR), it improved the CTR.
Effects on Renal Function: In anesthetized spontaneously hypertensive rats, cilnidipine increased the urinary volume, renal blood flow and glomerular filtration rate at the dose inducing hypotension. Cilnidipine also increased the urinary volume, renal blood flow and glomerular filtration rate, when the renal function was depressed by endothelin.
In patients with essential hypertension, cilnidipine did not affect renal function while the blood pressure was decreased.
Effect on Cardiovascular Disturbance Associated with Hypertension: In stroke-prone spontaneously hypertensive rats, a single daily dose of cilnidipine suppressed the appearance of stroke and improved the survival rate. In addition, it lessened cardiac hypertrophy (increased heart weight), thickening of the ventricular wall, myocardial fibrosis and lesions in the kidney. Moreover, it depressed medial thickening in the coronary arterial wall and decreased calcium content in the aorta.
In patients with essential hypertension, cilnidipine decreased the atherosclerotic index and serum lipid peroxide.

Telmisartan
In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours. Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid). In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

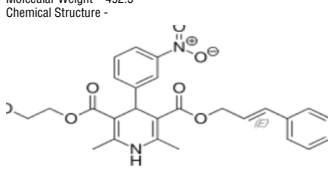
Pharmacokinetic properties
Cilnidipine
Plasma Drug Levels:
When a single dose of cilnidipine 5 mg, 10 mg or 20 mg cilnidipine was orally administered to 6 healthy male volunteers, the C_{max} was found to be 4.7 ng/mL, 5.4 ng/mL and 15.7 ng/mL, respectively and the $AUC_{0\text{-}24}$ to be 23.7ng·hr/mL, 27.5ng·hr/mL and 60.1ng·hr/mL, respectively. Thus, both parameters increased in a dose dependent manner.
When a single dose of cilnidipine 10 mg was repeatedly administered once a day to 6 healthy male volunteers, pharmacokinetic parameters of cilnidipine were indicated as follows.
The plasma concentration reached a steady-state from Day 4 of the administration and there was no evidence of the accumulation.
Metabolism and Excretion:
From the metabolites identified in the plasma and urine of healthy male volunteers, it is considered that the major route of cilnidipine metabolism is demethylation of the methoxyethyl group followed by hydrolysis of the cinnamyl ester and oxidation of the dihydropyridine ring. It is considered that CYP3A4 is mainly involved and CYP2C19 is partly involved in the demethylation of the methoxyethyl group (in vitro).
The calcium channel blocking action of the metabolite with the demethylated methoxyethyl group was only 1/00 of that of the parent compound (in rabbits).
When a single oral dose of cilnidipine 10 mg was repeatedly administered to healthy male volunteers once a day for 7 days, no unchanged compound of cilnidipine but 5.2% of the dose was excreted in the urine as metabolites. (The approved administration of cilnidipine is orally once a day after breakfast.)
An *in vitro* experiment showed that cilnidipine was 99.3% bound to human serum protein.

Telmisartan
Absorption: Following oral administration, peak concentrations (C_{max}) 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 mg and 160 mg, the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 mg 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 albumin and 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 and Elimination Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). 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. Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

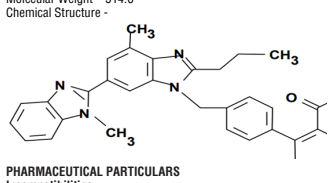
NONCLINICAL PROPERTIES
Carcinogenesis, Mutagenesis, Impairment of Fertility
Cilnidipine
No data available.

Telmisartan
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/m² basis, 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/m² basis, 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).

DESCRIPTION
This product (Cilnidipine/Telmisartan Tablet) is a fixed dose combination and contains cilnidipine and telmisartan as active ingredient. It is indicated for the treatment of essential hypertension.
Cilnidipine is a novel dihydropyridine calcium antagonist and its calcium antagonistic activity is lasting longer than those of Nifedipine and Nicardipine.
Molecular Formula – $C_{27}H_{28}N_2O_7$
Molecular Weight – 492.5
Chemical Structure -



Telmisartan is a non-peptide angiotensin II receptor (type AT1) antagonist.
Molecular Formula – $C_{33}H_{30}N_4O_2$
Molecular Weight – 514.6
Chemical Structure -



PHARMACEUTICAL PARTICULARS
Incompatibilities
None stated.

Shelf-life
Refer carton

Packaging information
Blister of 15 tablets

Storage and handing instructions
Store below 30°C.

PATIENT COUNSELLING INFORMATION
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Marketed by & ® Regd. Trade Mark of:
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai 400 030.

Note: This prescribing information is applicable for India Market only.

DATE OF REVISION
Feb 2025