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Telmisartan Tablets IP 20mg/40mg/80mg

TELMISAT® 20/40/80 टेलमिसेट 20/40/80

Composition:
TELMISAT® 20
Each uncoated tablet contains:
Telmisartan IP 20 mg
Excipients q.s.

TELMISAT® 40
Each uncoated tablet contains:
Telmisartan IP 40 mg
Excipients q.s.

TELMISAT® 80
Each uncoated tablet contains:
Telmisartan IP 80 mg
Excipients q.s.

WARNING
AVOID USE IN PREGNANCY
When used in pregnancy, 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.

Special Alerts:
ISSUE: A recently published study a meta-analysis combining cancer related findings from several clinical trials suggested use of angiotensin receptor blockers (ARBs) may be associated with a little increased risk of cancer

RECOMMENDATION: FDA has not concluded that ARBs increase the risk of cancer. The Agency is reviewing information related to this safety concern and will update the public when additional information is available. FDA believes the benefits of ARBs continue to outweigh their potential risks. For more information visit the FDA website.

PHARMACEUTICAL FORM
Tablets
PHARMACOLOGICAL PROPERTIES
ATC code: C09CA07

Drug Description:
Telmisartan is a non-peptide angiotensin I receptor antagonist which is very potent in inhibiting angiotensin II - AT_1 receptor subtype highly selectively. Its empirical formula is $C_{33}H_{30}N_6O_2$, its molecular weight is 514.63.

Clinical Pharmacology
Mechanism of Action:
Telmisartan has greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor subtype. Angiotensin II is the principal pressor agent of the renin-angiotensin system that helps in vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Telmisartan blocks the vasoconstrictor and aldosterone secretion effect of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues. Its action is therefore independent of the pathways for angiotensin II synthesis. Telmisartan does not bind to or block other hormone receptors or ion channels which have a role in cardiovascular regulation.

Pharmacodynamics:
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.

Pharmacokinetics:
The oral bioavailability of Telmisartan is dose dependent. Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Administration with food slightly reduces the bioavailability of 40 mg telmisartan by 6%, and about 20% after a 160 mg dose. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α1 - acid glycoprotein.

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine

Special Populations:
Pediatric: In patients <18 years of age, telmisartan pharmacokinetics have not been investigated.
Geriatric: The pharmacokinetics do not differ between the elderly and those younger than 65 years of telmisartan.
Renal Insufficiency: No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration.

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentration of telmisartan is increased and telmisartan should be initiated under close medical supervision in such patients.

Therapeutic Efficacy
A prospective, randomized, open-label, blinded end-point trial demonstrated that telmisartan 80 mg once daily was superior to valsartan 80mg once daily in reducing diastolic blood pressure during the last 6 hours of the 24- hour dosing interval. These results may be due to telmisartan's longer half-life or to a higher potency compared with valsartan, such that a higher dose of valsartan may produce effects similar to those of 80 mg telmisartan.

When compared with dihydropyridine calcium antagonist, beta adrenergic blockers, angiotensin-converting enzyme inhibitors and other angiotensin II receptor antagonists, telmisartan has been shown to be superior in diminishing ambulatory blood pressure throughout the 24- hour period between doses.

Three separate randomized, double-blind, parallel-group, 12-week trials compared telmisartan with enalapril, lisinopril and amlodipine for treating mild to moderate hypertension. Telmisartan demonstrated efficacy similar to lisinopril and greater efficacy than enalapril and amlodipine throughout the 24-hour dosing interval. Telmisartan was associated with a lower incidence of treatment related cough than lisinopril and enalapril and less treatment-related angioedema than amlodipine.

Indication:
Telmisartan is indicated for the treatment of Hypertension. It can be used individually or in combination with any other antihypertensive agents.

Dosage and Administration:
The usual starting dose of **TELMISAT®** tablets is 40 mg once a day. To give the full benefit of telmisartan to the patient, dose should be built up to TELMISAT 80mg per day.

Blood pressure response is dose related over the range of 20-80 mg. Maximum antihypertensive effect is generally attained at 4 to 8 weeks after start of treatment. Dosage must be individualized.

Dosage adjustments are not required on basis of age, gender or renal dysfunction (mild to moderate renal impairment). **TELMISAT®** should be used with caution in hepatic impairment, in whom dose should not exceed 40 mg/day, and in those with depleted intravascular volume.

TELMISAT® tablets may be administered with other antihypertensive agents.

TELMISAT® tablets may be administered with or without food.

Contraindication:
TELMISAT® (telmisartan) is contraindicated in patients who are hypersensitive to any component of this product.

Precautions:
Hepatic Insufficiency: Telmisartan is mainly eliminated by biliary excretion, hence can be expected to have reduced clearance in patients with hepatic impairment. Telmisartan must be given under close medical supervision in such patients.
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 Renal Function: In patients whose renal function may

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

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depend on the activity of the renin- angiotensin- aldosterone system, treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonist has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

Pregnancy: Drugs acting directly on the renin-angiotensin-aldosterone system are documented to cause fetal or neonatal injury or death when used during second or third trimester of pregnancy. Exposure to drug limited to the first trimester has not been associated with fetal or neonatal injury. However, when patients become pregnant, **TELMISAT®** should be discontinued as soon as possible.
Pregnancy Categories C (first trimester) and D (second and third trimesters).

Nursing Mothers: It is not known whether telmisartan is excreted in human milk, but telmisartan has shown presence in the milk of lactating rats. Due to probability of adverse events on the nursing infant, a decision to discontinue nursing or the drug should be taken in relation to the importance of the drug to the mother.

Pediatric Use:
Safety and efficacy in pediatric patients has not been established. Geriatric Use: No overall differences in efficacy and safety were observed in elderly patients compared to younger patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest dose administered to mice (1000mg/kg/day) and rats (100mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan.

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.

Adverse Reactions:
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 (20-160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo.

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, non-specific 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%).
Postmarketing Experience: The following adverse reactions have been identified during post-approval use of Telmisartan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Telmisartan.

The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including Telmisartan.

Drug Interactions: Telmisartan is not metabolized by any cytochrome P450 (CYP) isoenzymes, hence has low potential to interfere with metabolism of drugs, metabolized through this system.

Digoxin: Plasma concentration was altered during co-administration of telmisartan. However no interaction was reported in a large well designed study of telmisartan in heart failure in which more than one-third of patients were taking digoxin. Nonetheless, serum digoxin concentration should be monitored and dosage of digoxin adjusted accordingly when therapy with telmisartan is introduced.

Warfarin: Telmisartan had a little effect on plasma warfarin concentration in 12 healthy volunteers, but there was no statistically significant change in international normalized ratio (INR) after introduction of telmisartan.

Other drugs: Co-administration of telmisartan had no effect on steady state pharmacokinetics of amlodipine, glibenclamide, ibuprofen, paracetamol and hydrochlorothiazide

Over dosage: Limited data are available with respect to overdosage in human beings. The most likely manifestations due to over dosage of **TELMISAT®** can be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If sympotomatic, hypotension should involve supportive treatment. Hemodialysis is not capable of eliminating Telmisartan.

Shelf Life: Please refre carton/strip.

Storage: Store below 25°C, protect from light and moisture.
Keep out of reach of children.

Presentation:
TELMISAT®20 : strip of 10 tablets
TELMISAT®40 : strip of 10 tablets
TELMISAT®80 : strip of 10 tablets

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

BF/LL/3729/01

® - Registered trademark

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No: **1800 102 9465** or e mail us at **drugsafety@biocon.com**