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

TELDAY
(Telmisartan Tablets I.P.)

COMPOSITION:

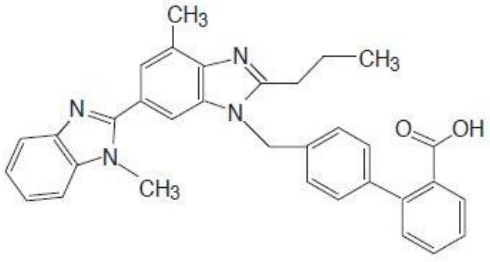
TELDAY-20
Each uncoated tablet contains:
Telmisartan I.P. 20 mg

TELDAY-40
Each uncoated tablet contains:
Telmisartan I.P. 40 mg

TELDAY-80
Each uncoated tablet contains:
Telmisartan I.P. 80 mg

WARNING: FETAL TOXICITY
When pregnancy is detected, discontinue the product as soon as possible.
Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

DESCRIPTION
Telmisartan is a nonpeptide angiotensin II receptor (type AT_1) antagonist. It is chemically described as 4'-[[4-Methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylicacid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.6 and its structural formula is as below.



CLINICAL PHARMACOLOGY
Mechanism of Action: Angiotensin ll is formed from angiotensin I in a reaction catalyzed by angiotensinconverting 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 ll by selectively blocking the binding of angiotensin ll to the AT_1 receptor in many tissues, such as

vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin ll synthesis. Telmisartan has much greater affinity (>3000 fold) for the AT_1 receptor than for the AT_2 receptor which is not known to be associated with cardiovascular homeostatics. Telmisartan does not inhibit ACE (kininase ll), hence it does not affect the response to bradykinin. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardio vascular regulation. Blockade of the angiotensin ll receptor inhibits the negative regulatory, feedback of angiotensin ll on rennin secretion, but the resulting increased plasma rennin activity and angiotensin ll circulating levels do not overcome the effect of Telmisartan on blood pressure.

Pharmacokinetics

General:

Following oral administration peak concentrations (C_{max}) of Telmisartan are reached in 0.5-1 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 40mg tablet and about 20% after a 160mg dose. The absolute bioavailability of Telmisartan is dose dependent. At 40 and 160mg, the bio availability was 42% and 58%, respectively. The pharmacokinetics of orally administered Telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows biexponential decay kinetics with a terminal elimination half life of approximately 24 hours. Through 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.

Metabolism and Elimination:

Following either intravenous or oral administration of 14C-labelled 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 acylglucuronide; 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 >800mL/min. Terminal half-life and total clearance appear to be independent of dose.

Distribution:

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and alpha1-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.

Special Population:

Pediatric:

Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric:

The pharmacokinetics of Telmisartan do not differ between the elderly and those younger than 65 years

Gender:
Plasma concentrations of Telmisartan are generally 2-3 times higher in females than in males. However, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Renal Insufficiency:
Renal excretion does not contribute to the clearance of Telmisartan. No dosage adjustment may be necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration.

Hepatic Insufficiency:
In patients with hepatic insufficiency, plasma concentrations of Telmisartan are increased, and absolute bio availability approaches 100%.

Pharmacodynamics
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.

Clinical Trials
The antihypertensive effects of Telmisartan have been demonstrated in six principal placebo controlled clinical trials, studying a range of 20-160 mg; one of these examined the antihypertensive effects of Telmisartan and hydrochlorothiazide in combination. The studies involved a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95-114 mmHg), 1031 of who were treated with Telmisartan Following once daily administration of Telmisartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

Upon initiation of antihypertensive treatment with Telmisartan, blood pressure was reduced after the first dose, with a maximal reduction by about 4 weeks. With cessation of treatment with Telmisartan tablets, blood pressure gradually returned to baseline values over a period of several

days to one week. During long term studies (without placebo control) the effect of Telmisartan appeared to be maintained for up to at least one year. The antihypertensive effect ofTelmisartan is not influenced by patient age, gender, weight or body mass index. Blood pressure response in black patients (usually a low-renin population) is noticeably less than that in Caucasian patients. This has been true for most, but not all, angiotensin II antagonists and ACE inhibitors. In a controlled study, the addition of Telmisartan to hydrochlorothiazide produced an additional dose-related reduction in blood pressure that was similar in magnitude to the reduction achieved with Telmisartan monotherapy. Hydrochlorothiazide also had an added blood pressure effect when added to Telmisartan. The onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. At doses of 20, 40, and 80 mg, the antihypertensive effect of once daily administration of Telmisartan is maintained for the full 24-hour dose interval. With automated ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24-hour trough-to-peak ratio for 40 - 80 mg doses of Telmisartan was 70-100% for both systolic and diastolic blood pressure. The incidence of symptomatic orthostasis after the first dose in all controlled trials was low (0.04%).There were no changes in the heart rate of patients treated with telmisartan in controlled trials.

INDICATIONS

Telday is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATION

Contraindicated in patients who are hypersensitive to any component of this formulation.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. **When pregnancy is detected, Telmisartan should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.** Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Telmisartan as soon as possible. Should the medication be continued, the mothers should

be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligohydramnios is observed, Telmisartan should be discontinued unless they are considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. There is no clinical experience with the use of Telmisartan in pregnant women. No teratogenic effects were observed when Telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day.

Hypotension in Volume-Depleted Patients
In patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients, symptomatic hypotension may occur after initiation of therapy with Telmisartan. This condition should be corrected prior to administration of Telmisartan, or treatment should start 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.

PRECAUTIONS
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; hence Telmisartan should be used with caution in these patients, with a smaller dosage.

Impaired Renal Function:
As a consequence of inhibiting the rennin-angiotensinaldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the rennin-angiotensin - aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme 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 may be anticipated in patients treated with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan tablets in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

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.

The reported 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 m^2).

Carcinogenesis, Mutagenesis, Impairment of Fertility
There was no evidence of carcinogenecity 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/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Telmisartan (80mg/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 coil (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/m_2 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).

Pregnancy
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 shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: 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.

DRUG INTERACTION
Digoxin:
Median increase in peak plasma concentration (49%) and trough concentration (20%) of digoxin is observed with coadministration of Telmisartan. It is, therefore, recommended that digoxin

levels be monitored when initiating, adjusting, and discontinuing Telmisartan to avoid possible over- or under-digitalization.

Warfarin:
Telmisartan administered for 10 days is reported to slightly decrease the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).

Other Drugs:
Coadministration of Telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, 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.

ADVERSE REACTIONS

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over six months and more than 1300 for over one year.

Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. In placebo-controlled trials involving 1041 patients treated with various doses of Telmisartan (20-160mg) monotherapy for up to 12 weeks, an overall incidence of adverse events similar to that of placebo was observed.

Adverse events occurring at an incidence of 1% or more in patients treated with Telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in the following table.

	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 due to 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 six 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, hypoaesthesia;

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 due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% Telmisartan patients compared with 0.3% placebo patients. One Telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with Telmisartan; all marked elevations occurred at a higher frequency with placebo. No Telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. The usual starting dose of Telmisartan is 40 mg once a day. Blood pressure response is dose related over the range of 20-80 mg. Most of the antihypertensive effect is apparent within two weeks and maximal reduction is generally attained after four weeks. When additional blood pressure reduction beyond that achieved with 80 mg Telmisartan is required, a diuretic may be added. No initial dosing 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 may be administered with or without food.

Special Populations:

Patients with depletion of intravascular volume:

Patients with depletion of intravascular volume should have the condition corrected or Telmisartan should be initiated under close medical supervision.

Patients with hepatic impairment: Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision.

Elderly/Patients with renal impairment: No initial dosing 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.

OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with Telmisartan 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 hemodialysis.

EXPIRY DATE

Do not use later than date of expiry.

STORAGE

Store at a temperature not exceeding 30^{o}C, protected from moisture. Keep out of reach of children

PRESENTATION
Telday 20, 40 and 80 mg tablets are available in blister strip of 15 tablets.

MARKETED BY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IN/TELDAY 20,40,80mg/MAR-16/03/PI