For the use of a Registered Medical Practitioner or a Hospital or a Laboratory xxxxxxxx-5103

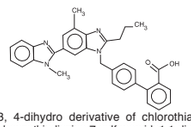
TELDAY-H

TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLETS

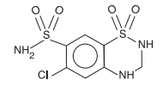
COMPOSITION :
TELDAY-H:
Each uncoated bilayered tablet contains :
Telmisartan Ph. Eur. 40 mg
Hydrochlorothiazide I.P. 12.5 mg

DESCRIPTION

Telmisartan is a non-peptide Angiotensin II receptor (type AT1) antagonist. Telmisartan is chemically described as 4'-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol -1-yl] methyl]biphenyl-2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$.
Its molecular weight is 514.6 and its structural formula is:



Hydrochlorothiazide is the 3, 4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2H-1,2, 4-benzothiadiazine-7-sulfonamide1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$. Its molecular weight is 297.7 and its structural formula is:



Telmisartan is a white to slightly yellowish crystalline powder. It is practically insoluble in water and slightly soluble in methanol, sparingly soluble in methylene chloride. Hydrochlorothiazide is a white or almost white, odorless, crystalline powder. It is very slightly soluble in water and soluble in acetone, sparingly soluble in ethanol; dissolve in dilute solution of alkali hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action 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 re-absorption 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 rennin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Mechanism of Action Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte re-absorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increase in plasma renin activity, increase in aldosterone secretion, increase in urinary potassium loss and decrease in serum potassium. The mechanism of the antihypertensive effect of thiazides is not fully understood.

PHARMACOKINETICS

Telmisartan:

Absorption

Following oral administration, peak concentrations (Cmax) 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 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 of 20-160 mg, with greater than proportional increases of plasma concentrations with increasing doses.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and 1-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 Excretion

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 >800 ml/min. Terminal half-life and total clearance appear to be independent of dose.

Hydrochlorothiazide:

After oral dose, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percentage of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS

Fixed dose combination of Telmisartan and Hydrochlorothiazide is indicated for the treatment of Hypertension.

DOSAGE AND ADMINISTRATION

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. Patients with depletion of intravascular volume should have the condition corrected or telmisartan tablets should be initiated under close medical supervision (see WARNINGS, Hypotension in Volume Depleted Patients). Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision (see PRECAUTIONS). Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily. The recommended dose of Telday-H tablets is once a day. Telday-H can be administered with other antihypertensives. Telday-H can be administered with or without food.

CONTRAINDICATIONS

- Telday-H tablet is contraindicated in patients who are hypersensitive to any component of this product.
- This product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide - derived drugs because of hydrochlorothiazide component of product.
- Second and third trimesters of pregnancy.
- Cholestasis and biliary obstructive disorders.
- Severe hepatic impairment.Severe renal impairment (creatinine clearance <30 ml/min).
- Refractory hypokalaemia, hypercalcaemia.

WARNINGS

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Telday-H (telmisartan and hydrochlorothiazide) tablets should be discontinued as soon as possible (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Telmisartan

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 as it can cause injury and death to the developing foetus, when used in pregnancy during second and third trimester of pregnancy. 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 intra-amniotic 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.

Hydrochlorothiazide

Hepatic Impairment: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction: Lithium generally should not be given with thiazides.

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

PRECAUTIONS

Serum Electrolytes

Telmisartan and Hydrochlorothiazide

In controlled trials using the telmisartan/hydrochlorothiazide combination treatment, no patient administered 40/12.5 mg, 80/12.5 mg or 80/25 mg had a decrease in potassium ≥1.4 mEq/L, and no patient experienced hyperkalemia. No discontinuations due to hypokalemia occurred during treatment with the telmisartan/hydrochlorothiazide combination. The absence of significant changes in serum potassium levels may be due to the opposing mechanisms of action of telmisartan and hydrochlorothiazide on potassium excretion on the kidney.

Hydrochlorothiazide

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient experiences excessive vomiting or receives parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the post sympathectomy patient.If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Hepatic Function

Telmisartan

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. Telmisartan and hydrochlorothiazide tablets should therefore be used with caution in these patients.

Impaired Renal Function

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated 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), 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 in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Dual Blockade of the Renin-angiotensin-aldosterone System

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin - angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function. The ONTARGET trial enrolled 25,620 patients >55 years old with atherosclerotic disease or diabetes with end-organ damage, randomized 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 on the composite endpoint of cardiovascular death, myocardial infarction, stroke and heart failure hospitalization compared to monotherapy, but experienced an increased incidence of clinically important renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Co-administration of telmisartan and ramipril increases the exposure to both ramipril and ramiprilat by a factor of about 2. Concomitant use of telmisartan and ramipril is not recommended.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Telmisartan

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/m2 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/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).

Hydrochlorothiazide

There was no evidence of carcinogenicity when hydrochlorothiazide was administered in the diet

to mice and rats. Genotoxicity assays did not reveal any hydrochlorothiazide related effects at either the gene or chromosome level.

Carcinogenicity:

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

Pregnancy

Telmisartan

Pregnancy Categories C (first trimester) and D (second and third trimesters) (see WARNINGS, **Fetal/Neonatal Morbidity and Mortality)**

Hydrocholorothiazide

Pregnancy Category B

Nursing Mothers

Telmisartan

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.

Hydrochlorothiazide

Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, 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 INTERACTIONS

General

Medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives): If these substances are to be prescribed with the hydrochlorothiazide - telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium. Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporin or other medicinal products such as heparin sodium): If these medicinal products are to be prescribed with the hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the renin-angiotensin system, concomitant use of the above medicinal products may lead to increases in serum potassium and is, therefore, not recommended. Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when telmisartan and hydrochlorothiazide combination is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes inducing medicinal products (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes.

- class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine IV.)

Based on their pharmacological properties it can be expected that the following medicinal product may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine.

Telmisartan

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. 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 slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).

Other Drugs: Co-administration 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.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists including telmisartan. Because lithium should not be used with diuretics, the use of lithium with telmisartan and hydrochlorothiazide is not recommended.

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.

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.

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressure amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Telday-H.

Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Telday-H and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia favours the onset of digitalis induced arrhythmia.

Metformin: Metformin should be used with precaution: risk of lactic acidosis induced by a possible functional renal failure linked to hydrochlorothiazide.

Medicinal products used in the treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol): Dosage adjustment of uricosuric medications may be necessary as hydro-chlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide may increase the incidence of hypersensitivity reactions of allopurinol.

Calcium salts: Thiazide diuretics may increase serum calcium levels due to the decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Beta-blockers and diazoxide: The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Amantadine: Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate): Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

ADVERSE EFFECTS

Fixed Dose Combination of Telmisartan & hydrochlorothiazide has been evaluated for safety in over 1700 patients, including 716 treated for over six months and 420 for over one year. In clinical trials with Fixed Dose Combination of Telmisartan & hydrochlorothiazide, no unexpected adverse events have been observed. Adverse experiences have been limited to those that have been previously reported with telmisartan and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. Most adverse experiences were mild in intensity and transient in nature and did not require discontinuation of therapy. Adverse events occurring at an incidence of 2% or more in patients treated with telmisartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

Tabel-1: Adverse Events occurring in ≥ 2% of Telmisartan / Hydrochlorothiazide (HCTZ) Patients*

	Telmisartan + HCTZ	Placebo	Telmisartan	HCTZ
Body as whole				
Fatigue	3	1	3	3
Influenza like symptom	2	1	2	3
CNS/PNS				
Dizziness	5	1	4	6
Gastrointestinal System				
Diarrhoea	3	0	5	2
Nausea	2	0	1	2
Respiratory disorder				
Sinusitis	4	3	3	6
Upper respiratory tract infection	8	7	7	10

*includes all doses of telmisartan (20-160 mg), hydrochlorothiazide (6.25-25 mg), and combinations there of
CNS - Central Nervous System PNS- Peripheral Nervous System

The following adverse events were reported at a rate less than 2% in patients treated with telmisartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo: back pain, dyspepsia, vomiting, tachycardia, hypokalemia, bronchitis, pharyngitis, rash, hypotension postural, abdominal pain. Finally, the following adverse events were reported at a rate of 2% or greater in patients treated with telmisartan/hydrochlorothiazide, but were as, or more common in the placebo group: pain, headache, cough, urinary tract infection. Adverse events occurred at approximately the same rates in men and women, older and younger patients, and black and non-black patients.

Telmisartan

Other adverse experiences that have been reported with telmisartan, without regard to causality, are listed below:

Autonomic Nervous System: impotence, increased sweating, flushingBody as a Whole: allergy, fever, leg pain, malaise, chest pain

Cardiovascular: palpitation, dependent edema, angina pectoris, leg edema, abnormal ECG, hypertension, peripheral edema

CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia

Gastrointestinal: flatulence, constipation, gastritis, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders

Metabolic: gout, hypercholesterolemia, diabetes mellitus.

Musculoskeletal: arthritis, arthralgia, leg cramps, myalgiaPsychiatric: anxiety, depression, nervousness

Resistance Mechanism: infection, fungal infection, abscess, otitis media.

Respiratory: asthma, rhinitis, dyspnea, epistaxis

Skin: dermatitis, eczema, pruritus

Urinary: micturition frequency, cystitis.

Vascular: cerebrovascular disorder.

Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

A single case of angioedema was reported (among a total of 3781 patients treated with telmisartan).

Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a whole: weakness

Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation.

Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

Metabolic: hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: muscle spasm

Nervous System/Psychiatric: restlessness.

Renal: renal failure, renal dysfunction, interstitial nephritis.

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis.

Special Senses: transient blurred vision, xanthopsia.

Other adverse effects: bronchitis, pharyngitis, sinusitis, sleep disorder, visual disturbances, hyperhidrosis, limb pain, Influenza-like illness, creatinine phosphokinase increased.

OVERDOSAGE

There is limited information available for telmisartan with regard to overdose in humans.The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

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

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment: Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store below 30°C, protected from moisture.

PRESENTATION

TELDAY-H is available in strip of 10 tablets.

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Baddi 173 205, Dist. Solan (H.P.) INDIA.