

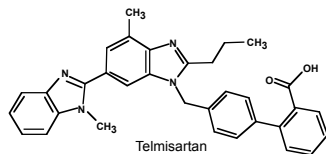
CoTasmi™

(Telmisartan + Hydrochlorothiazide)

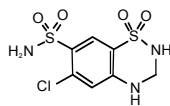
40mg+12.5mg, 80mg+12.5mg Tablets

DESCRIPTION

CO TASMI (Telmisartan + Hydrochlorothiazide) is a combination of telmisartan, an orally active angiotensin II antagonist, and hydrochlorothiazide, a diuretic. Telmisartan is chemically described as 4'-[1, 4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazo [1,1'-y]methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its molecular formula is C₃₃H₃₀N₄O₂, its structural formula is:



Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide. Its molecular formula is C₇H₈ClN₂O₄S₂, its structural formula is:



Hydrochlorothiazide

QUANTITATIVE & QUALITATIVE COMPOSITION

CO TASMI (Telmisartan + Hydrochlorothiazide) Tablets are available for oral administration as:

CO TASMI (Telmisartan + Hydrochlorothiazide) Tablets 40mg+12.5mg
Each tablet contains:
Telmisartan USP... 40mg
Hydrochlorothiazide USP... 12.5mg

CO TASMI (Telmisartan + Hydrochlorothiazide) Tablets 80mg+12.5mg
Each tablet contains:
Telmisartan USP... 80mg
Hydrochlorothiazide USP... 12.5mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Telmisartan
Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT₁) antagonist. 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. In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. Telmisartan has much greater affinity (>3,000 fold) for the AT₁ receptor than for the AT₂ receptor.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with thiazide diuretics.

Pharmacokinetics

Telmisartan

Telmisartan is rapidly absorbed from the gastrointestinal tract; the absolute oral bioavailability is dose-dependent and is about 42% following a 40mg dose and 58% following a 160mg dose. Peak plasma concentration of telmisartan is reached about 0.5 to 1.5 hours after an oral dose. 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. Telmisartan is over 99% bound to plasma proteins. It is excreted almost entirely in the feces via bile, mainly as unchanged drug. The terminal elimination half-life of telmisartan is about 24 hours. Telmisartan does not accumulate significantly in plasma on repeated administration.

Hydrochlorothiazide

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65-70%. Peak plasma concentrations of hydrochlorothiazide are reached in approximately 1 to 2.5 hours after dosing. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells.

It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

Special Populations

Pediatric

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

Renal Impairment

Telmisartan

In mild to moderate and severe renal impairment doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal impairment undergoing dialysis. In patients with mild to moderate renal impairment (creatinine clearance of 30-60mL/min, mean about 50mL/min) no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Hydrochlorothiazide

In patients with impairment renal function the rate of hydrochlorothiazide elimination is reduced. In functionally anephric patients the elimination half life is about 34 hours.

Hepatic Impairment

Telmisartan

In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased and absolute bioavailability approaches 100%.

THERAPEUTIC INDICATIONS

CO TASMI (Telmisartan + Hydrochlorothiazide) is indicated for the treatment of hypertension.

This fixed dose combination is not indicated for initial therapy.

DOSAGE AND ADMINISTRATION

- It is usually appropriate to begin combination therapy only after a patient failed to achieve desired effect with monotherapy.
- CO TASMI (Telmisartan + Hydrochlorothiazide) can be taken with or without meals.
- CO TASMI (Telmisartan + Hydrochlorothiazide) may be administered with other anti-hypertensive agents.
- Usually effective dose of telmisartan is 40mg once daily. Blood response is dose related over the range of 20-80mg. Some patients may already benefit at a daily dose of 20mg.
- Hydrochlorothiazide is effective in doses of 12.5mg to 50mg once daily.

Renal impaired patients

The usual regimens of therapy with CO TASMI (Telmisartan + Hydrochlorothiazide) may be followed as long as the patient's creatinine clearance is >30mL/min. In patients with more severe renal impairment it is not recommended to use thiazide.

Hepatic impaired patients

In patients with mild to moderate hepatic impairment the dosage should not exceed 40mg+12.5mg once daily.

ADVERSE REACTIONS

Adverse reactions occurring with both telmisartan + hydrochlorothiazide include:

Common: Dizziness

Uncommon: Hypokalemia, anxiety, syncope, paraesthesia, vertigo, tachycardia, arrhythmias, hypotension, or thostatic hypotension, dyspnoea, diarrhea, dry mouth, flatulence, back pain, muscle spasms, myalgia, erectile dysfunction, chest pain and blood uric acid increase.

Rare: Bronchitis, hyperuricemia, hyponatremia, depression, insomnia, sleep disorders, visual disturbance, vision blurred, respiratory distress, abdominal pain, constipation, dyspepsia, vomiting, abnormal hepatic function/liver disorder, angioedema, muscle cramp, pain in limb, influenza-like illness, pain, blood creatinine increased, blood creatine phosphokinase increased and hepatic enzyme increased.

As with other angiotensin II antagonists isolated cases of angioneurotic edema, urticaria and other related reactions have been reported.

Laboratory findings:

Hemoglobin and Hematocrit: Decreases in hemoglobin ($\geq 2g/dL$) and hematocrit ($\geq 9\%$).

Creatinine, Blood Urea Nitrogen (BUN): Increase in BUN ($\geq 11.2mg/dL$) and serum creatinine ($\geq 0.5mg/dL$).

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred.

CONTRAINDICATIONS

Telmisartan + Hydrochlorothiazide combination is contraindicated:

- In patients who are hypersensitive to this drug or any component of this product.
- In patients with anuria or hypersensitivity to other sulfonamide-derived drugs, due to hydrochlorothiazide component in the preparation.
- Refractory hypokalemia and hypercalcaemia.
- During second and third trimesters of pregnancy and lactation.
- With cholestasis and biliary obstructive disorders.

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- With severe hepatic impairment.
- With severe renal impairment.

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, CO TASMI (Telmisartan + Hydrochlorothiazide) tablets should be discontinued as soon as possible.

PRECAUTIONS

Hepatic impairment: Telmisartan + Hydrochlorothiazide 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.

Renovascular hypertension: There is an increased risk of severe hypotension and renal impairment when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation: There is less experience in patients with mild to moderate renal impairment, therefore, periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Thiazide diuretic-associated azotemia may occur in patients with impaired renal function.

Intravascular hypovolemia: Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhea or vomiting. Such conditions should be corrected before the administration of telmisartan + hydrochlorothiazide.

Stimulation of the renin-angiotensin-aldosterone system: In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, hyperazotemia, oliguria or rarely acute renal failure.

Primary aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Telmisartan + Hydrochlorothiazide is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy.

Metabolic and endocrine effects: Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Increase in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Electrolyte imbalance: For any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hyperkalemia, hypokalemia, hyponatremia, hypochloremic alkalosis, hypercalcemia, hypomagnesemia).

Others:

- As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.
- Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of hypersensitivity or bronchial asthma, but are more likely in patients with such a history.
- Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.
- When driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.
- Cases of photosensitivity reactions have been reported with thiazide diuretics. If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Nursing Mothers

Telmisartan + Hydrochlorothiazide is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Thiazides appear in human milk and may inhibit lactation.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Drug Interactions

Lithium: Coadministration of lithium and telmisartan + hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Digoxin: It is recommended that digoxin level be monitored when initiating, adjusting and discontinuing telmisartan to avoid over- or under-digitalization.

Medicinal products associated with potassium loss and hypokalemia (e.g., other kalluretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives), Medicinal

products that may increase potassium levels or induce hyperkalemia (e.g., ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporine or other medicinal products such as heparin sodium): If these medicinal products are to be prescribed with the telmisartan + hydrochlorothiazide combination, monitoring of potassium plasma levels is advised.

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when telmisartan + hydrochlorothiazide is administered with these medicinal products affected by serum potassium disturbances: class Ia antiarrhythmics (e.g., quinidine, hydroquinidine, disopyramide), class III antiarrhythmics (e.g., amiodarone, sotalol, dofetilide, ibutilide), some antipsychotics (e.g., thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulpitride, amisulpride, tiapride, pimozide, haloperidol, droperidol), others (e.g., bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparflaxacin, tefenadine, vincamine IV.).

Anti-diabetic medicinal products (oral agents and insulin): Dosage adjustment of the anti-diabetic medicinal products may be required.

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

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Non-steroidal anti-inflammatory medicinal products: NSAIDs (i.e., acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics and the antihypertensive effects of angiotensin II antagonists. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the coadministration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

Medicinal products used in the treatment for gout (e.g., probenecid, sulfapyrazone and allopurinol): Dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfapyrazone may be necessary. Coadministration 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: The hyperglycemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Anticholinergic agents (e.g., atropine, biperiden) it 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.

OVERDOSAGE

The most likely manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur. Overdose with hydrochlorothiazide is associated with electrolyte depletion and dehydration resulting from excessive diuresis.

The patient should be closely monitored. 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.

HOW SUPPLIED

CO TASMI (Telmisartan + Hydrochlorothiazide) Tablets 40mg+12.5mg are available in blister pack of 14's.

CO TASMI (Telmisartan + Hydrochlorothiazide) Tablets 80mg+12.5mg are available in blister pack of 14's.

STORAGE

Store at 25°C (Excursions permitted between 15°C - 30°C). Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:



Getz
pharma
(PVT) LIMITED
www.getzpharma.com

29-30/27,
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Pakistan

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