TELEXA®-80 H

PRODUCT DESCRIPTION:

TELEXA® - 80 H Tablets:

Each tablet contains,
Telmisartan – 80 mg
Hydrochlorothiazide – 12.5 mg

Rx only
Prescribing Information

WARNING: FETAL TOXICITY

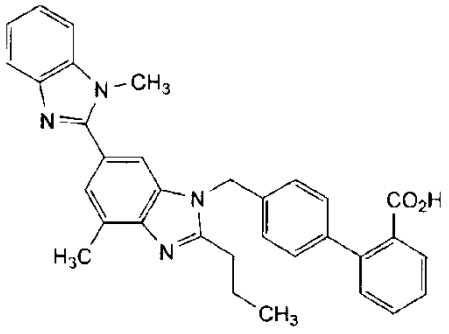
- When pregnancy is detected, discontinue TELEXA®- 80 H tablets as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (see WARNINGS, Fetal/Neinatal Toxicity).

DESCRIPTION:

TELEXA®-80 H tablets are a combination of telmisartan, an orally active angiotensin II antagonist acting on the AT_1 receptor subtype, and hydrochlorothiazide, a diuretic of thiazide class.

Telmisartan

Structural formula:



Molecular formula: $C_{33}H_{30}N_4O_2$

Chemical name:
4'-[[4-Methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl] methyl] bi phenyl-2-carboxylic acid

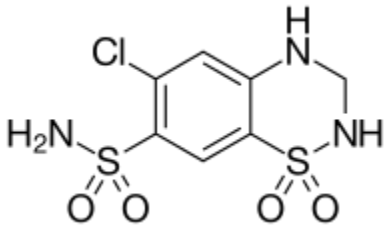
Molecular weight: 514.6 g/mol

pKa: 4.45

Telmisartan is a specific non-peptide angiotensin II receptor (type AT1) antagonist. Telmisartan is a white or slightly yellowish crystalline powder. It is practically insoluble in water, slightly soluble in methanol and sparingly soluble in methylene chloride.

Hydrochlorothiazide

Structural formula:



Molecular formula: $C_7H_8ClN_3O_4S_2$

Chemical name:

6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide

Molecular weight: 297.74 g/mol

Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water, and freely soluble in sodium hydroxide solution.

TELEXA®-80 H tablet is formulated for oral administration, tablet availble as 80 mg/12.5 mg telmisartan and hydrochlorothiazide. TELEXA®-80 H tablets are hygroscopic and require protection from moisture.

PHARMACOLOGIC PROPERTIES:

PHARMACODYNAMICS

Telmisartan:

Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II.

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone- secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure

In addition to blocking the RAS, telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism. It is believed that telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovasculr disease (CVD).

Telmisartan has a PPARγ agonist activity. Its activity at the peroxisome proliferator-activated receptor delta (PPAR-δ) receptor has prompted speculation around its potential. Telmisartan activates PPAR-δ receptors in several tissues.

In humans, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked increase in blood pressure. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

After administration of the first dose of telmisartan, onset of antihypertensive activity occurs gradually within 3 hours. The maximal reduction in blood pressure is generally attained 4-8 weeks after the start of treatment. With 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% for both systolic and diastolic blood pressure.

In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan is independent of gender or age, and has been compared to antihypertensive drugs including amlodipine, atenolol, enalapril, ramipril, hydrochlorothiazide, lisinopril and valsartan. Telmisartan (40-120 mg once daily) is at least as effective as amlodipine (5-10 mg) and atenolol (50-100 mg once daily). Telmisartan (20-80 mg once daily) is equivalent to enalapril (5-20 mg once daily), and telmisartan (40-160 mg once daily) is comparable to lisinopril (10-40 mg once daily).

Upon abrupt cessation of treatment, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

Hydrochlorothiazide:

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in

about 4 hours and lasts about 6 to 12 hours.

PHARMACOKINETICS

Absorption

Telmisartan

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Telmisartan is quickly but to varying degrees absorbed from the gut. The average bioavailability is about 50% (42–100%). 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 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Hydrochlorothiazide

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.

Distribution

Telmisartan

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and $\alpha 1$-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.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Metabolism & Excretion

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

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours.

SPECIAL POPULATIONS

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

Geriatric: The pharmacokinetics of telmisartan does not differ between the elderly and those younger than 65 years (see DOSAGE AND ADMINISTRATION).

Gender: Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, 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. Based on modest experience in patients with mild-to-moderate renal impairment (creatinine clearance of 30-80 mL/min, mean clearance approximately 50 mL/min), no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

INDICATIONS

TELEXA®-80 H tablets are indicated for the treatment of hypertension (High blood pressure). This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

TELEXA®-80 H tablets are contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, hydrochlorothiazide, or any other component of this product (see ADVERSE REACTIONS).

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs. TELEXA®-80 H is contraindicated in Pregnancy & Lactation.

Do not co-administer aliskiren with TELEXA®-80 H in patients with diabetes (see PRECAUTIONS, Drug Interactions).

PRECAUTIONS

Serum Electrolytes

Telmisartan and Hydrochlorothiazide

In controlled trials using the telmisartan/hydrochlorothiazide combination treatment, no patient administered 80/12.5 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).

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. TELEXA®-80 H (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

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The **ONTARGET** trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, 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.

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 TELEXA®-80 H and other agents

that affect the RAS.

Do not co-administer aliskiren with TELEXA®-80 H in patients with diabetes. Avoid concomitant use of aliskiren with TELEXA®-80 H in patients with renal impairment (GFR <60 mL/min/1.73 m^2).

Co-administration of telmisartan and ramipril increases the exposure to both ramipril and ramiprilat by a factor of about 2 (see PRECAUTIONS, Drug Interactions).

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to TELEXA®-80 H during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension: A patient receiving TELEXA®-H80 (telmisartan and hydrochlorothiazide) tablets should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, TELEXA®-80 H tablets should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: A patient receiving TELEXA®-80 H tablets should be told not to use potassium supplements or salt substitutes that contain potassium without consulting the prescribing physician.

WARNINGS

Telmisartan Pregnancy Category: D

Hydrochlorothiazide Pregnancy Category: B

Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue TELEXA®-80 H as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin- angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue TELEXA®-80 H, unless it is

considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to TELEXA®-80 H for hypotension, oliguria, and hyperkalemia (see PRECAUTIONS, Pediatric Use).

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on an mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/ m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on an mg/ m^2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

Studies in which hydrochlorothiazide was administered to pregnant mice and rats during their periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume-Depleted Patients

Initiation of antihypertensive therapy in patients whose renin-angiotensin system is activated such as patients who are intravascular volume- or sodium-depleted, e.g., in patients treated vigorously with diuretics, should only be approached cautiously. These conditions should be corrected prior to administration of TELEXA®-80 H (telmisartan and hydrochlorothiazide) tablets. Treatment should be started under close medical supervision (see DOSAGE AND ADMINISTRATION). If hypotension occurs, the patients 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 (see **PRECAUTIONS**, **Drug Interactions**, ***Hydrochlorothiazide***, *Lithium*).

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.

INTERACTIONS WITH OTHER MEDICINES

Telmisartan

Aliskiren: Do not co-administer aliskiren with TELEXA®-80 H in patients with diabetes. Avoid use of aliskiren with TELEXA®-80 H in patients with renal impairment (GFR <60 mL/min).

***Digoxin*:** When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.

***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 C_{max} and AUC of ramipril 2.3

and 2.1 fold, respectively, and C_{max} and AUC of ramiprilat 2.4 and 1.5 fold, respectively. In contrast, C_{max} 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.

***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.

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 pressor 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 TELEXA®-80 H (telmisartan and hydrochlorothiazide) tablets.

***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 TELEXA®-80 H tablets 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Telmisartan and Hydrochlorothiazide

No carcinogenicity, mutagenicity, or fertility studies have been conducted with the combination of telmisartan and hydrochlorothiazide.

Telmisartan

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on an 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).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, in the Mouse Lymphoma Cell (mutagenicity) assay, and in the *Aspergillus nidulans* non-disjunction assay.

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.

Nursing Mothers

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Thiazides appear in human milk. 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

Neonates with a history of in utero exposure to TELEXA®-H:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In older age patients, 65-75 years of age or older has no overall differences in effectiveness and safety of telmisartan/hydrochlorothiazide were found in compared to younger patients. 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.

ADVERSE EFFECTS

TELEXA®-80 H (telmisartan and hydrochlorothiazide) tablets has following adverse events were reported lesser 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 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, flushing

Body as a Whole: allergy, fever, leg pain, malaise, chest pain

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

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, myalgia
Psychiatric: 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

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

POST-MARKETING EXPERIENCE

The following adverse reactions have been identified during post-approval use of TELEXA® (telmisartan) tablets. 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 TELEXA® tablets. 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, tendon pain (including tendonitis, tenosynovitis), drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome).

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

Clinical Laboratory Findings

In controlled trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of TELEXA®-80 H tablets.

Hemoglobin and Hematocrit: Decreases in hemoglobin (≥2 g/dL) and hematocrit (≥9%) were observed in 1.2% and 0.6% of telmisartan/hydrochlorothiazide patients, respectively, in controlled trials. Changes in hemoglobin and hematocrit were not considered clinically significant and there were no discontinuations due to anemia.

Creatinine, Blood Urea Nitrogen (BUN): Increases in BUN (≥11.2 mg/dL) and serum creatinine (≥0.5 mg/dL) were observed in 2.8% and 1.4%, respectively, of patients with essential hypertension treated with TELEXA®-80 H tablets in controlled trials. No patient discontinued treatment with TELEXA®-80 H tablets due to an increase in BUN or creatinine.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. No telmisartan/hydrochlorothiazide treated patients discontinued therapy due to abnormal hepatic function.

Serum Electrolytes: See PRECAUTIONS.

DOSAGE AND ADMINISTRATION

Treatment of Hypertension:

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.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The side effects (see WARNINGS) of telmisartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose- independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any

combination of telmisartan and hydrochlorothiazide will be associated with both sets of dose- independent side effects.

TELEXA®-80 H (telmisartan and hydrochlorothiazide) tablets may be administered with other antihypertensive agents.

TELEXA®-80 H tablets may be administered with or without food.

Replacement Therapy

The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect

TELEXA®-80 H tablets containing telmisartan 80 mg and hydrochlorothiazide 12.5 mg. A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg (see above) may be switched to TELEXA®-80 H tablets, telmisartan 80 mg/hydrochlorothiazide 12.5 mg once daily, and finally titrated up to 160/25 mg, if necessary.

A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide may be switched to TELEXA®-80 H (telmisartan 80 mg/hydrochlorothiazide 12.5 mg) tablets once daily. The clinical response to TELEXA®-80 H tablets should be subsequently evaluated and if blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to 160/25 mg, if necessary. Those patients controlled by 25 mg hydrochlorothiazide but who experience hypokalemia with this regimen, may be switched to TELEXA®-80 H (telmisartan 80 mg/hydrochlorothiazide 12.5 mg) tablets once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response.

Patients with Renal Impairment

The usual regimens of therapy with TELEXA®-80 H (telmisartan and hydrochlorothiazide) tablets may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so TELEXA®-80 H tablets are not recommended.

Patients with Hepatic Impairment

TELEXA®-80 H tablets are not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using lower dose of TELEXA®-80 H (see PRECAUTIONS).

OVERDOSAGE

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations 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.

Hydrochlorothiazide

The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

STORAGE CONDITION: Store at 25°C (77°F) in dry place; excursions permitted to 15°-30°C (59°-86°F). Keep out of reach of children.

PRESENTATION: Telmisartan 80mg + Hydrochlorothiazide 12.5 mg Tablets

PACKING: 1*10 TAB

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Gujarat-India
www.bioslab.co.in