CRESAR CT Tablets (Telmisartan + Chlorthalidone)

Composition

CRESAR CT 40

Each bilayer tablet contains:

Telmisartan.....40 mg

Chlorthalidone.....12.5 mg

CRESAR CT 80

Each bilayer tablet contains:

Telmisartan.....80 mg

Chlorthalidone.....12.5 mg

Dosage Form

Tablets

Description

CRESAR CT is a fixed-dose combination of telmisartan, an orally active angiotensin receptor blocker (ARB) acting on the angiotensin II type 1 (AT_1) receptor, and chlorthalidone, a thiazide-like diuretic. The two drugs target two separate mechanisms involved in blood pressure regulation and hence may provide additive blood pressure reduction.

Pharmacology

Pharmacodynamics

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 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. 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 renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations, with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after a single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple-dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, high-density and low-density lipoprotein cholesterol, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide

12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Chlorthalidone

Chlorthalidone is a benzothiadiazine (thiazide)-related diuretic with a long duration of action. Thiazide and thiazide-like diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting $NaCl^-$ reabsorption (by antagonising the Na^+Cl^- cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+ and water to the cortical collection tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.

In persons with normal renal function, diuresis is induced after the administration of 12.5mg chlorthalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose dependent and occur both in normal and in edematous patients. The diuretic effect sets in after 2 to 3 hours, reaches its maximum after 4 to 24 hours, and may persist for 2 to 3 days.

Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may possibly become activated.

In hypertensive individuals, chlorthalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral

resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of chlorthalidone is dose dependent between 12.5 and 50mg/day. Raising the dose above 50mg increases metabolic complications and is rarely of therapeutic benefit.

As with other diuretics, when chlorthalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomised clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics, including chlorthalidone, reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.

Combined treatment with other antihypertensives potentiates the blood-pressure lowering effects. In the large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.

In renal diabetes insipidus, chlorthalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated.

Pharmacokinetics

Absorption

Telmisartan

Following oral administration, peak concentrations 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 of about 6% with the 40mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose-dependent. At 40 mg and 160 mg, the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range of 20-160 mg, with greater than proportional increases of plasma concentrations 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 1.5-2.0 upon repeated once daily dosing.

Chlorthalidone

The bioavailability of an oral dose of 50mg chlorthalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50mg, C_{max} values average 1.5µg/ml (4.4µmol/L) and 3.2µg/ml (9.4µmol/L) respectively. For doses up to 100mg there is a proportional increase in AUC. On repeated daily doses of 50mg, mean steady-state blood concentrations of 7.2µg/ml (21.2µmol/L), measured at the end of the 24 hour dosage interval, are reached after 1 to 2 weeks.

Distribution

Telmisartan

Telmisartan is highly bound to plasma proteins (more than 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.

Chlorthalidone

In blood, only a small fraction of chlorthalidone is free, due to extensive accumulation in erythrocytes and binding to plasma proteins. Owing to the large degree of high affinity binding to the carbonic anhydrase of erythrocytes, only some 1.4% of the total amount of chlorthalidone in whole blood was found in plasma at steady state during treatment with 50mg doses. In vitro, plasma protein binding of chlorthalidone is about 76% and the major binding protein is albumin.

Chlorthalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50mg chlorthalidone daily before and after delivery, chlorthalidone levels in fetal whole blood are about 15% of those found in maternal blood.

Chlorthalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Metabolism and Elimination

Telmisartan

Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (more than 97%) was eliminated unchanged in the 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 acyl glucuronide; 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 more than 800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Chlorthalidone

Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and the feces, mainly in unchanged form. Chlorthalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlorthalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.

Special Populations

Pediatric

The pharmacokinetics of telmisartan has not been investigated in patients less than 18 years of age.

Geriatric

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

The elimination of chlorthalidone in elderly patients is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlorthalidone.

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 Impairment

No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration. Limited experience is available in patients with severe renal impairment or hemodialysis. A lower starting dose of 20 mg is recommended in these patients.

Renal dysfunction does not alter the pharmacokinetics of chlorthalidone as well, the rate-limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes.

Hepatic Impairment

In patients with hepatic impairment, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%. Telmisartan is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment, the posology should not exceed 40 mg once daily.

Indication

CRESAR CT is indicated for the treatment of essential hypertension, to lower blood pressure:

- In patients not adequately controlled with monotherapy
- As initial therapy in patients likely to need multiple drugs to help achieve blood pressure goals

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily stroke and myocardial infarction.

Dosage and Administration

Dosage must be individualized. The usual initial dosage is one tablet of **CRESAR CT 40** taken orally once daily.

A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 40 mg may be switched to **CRESAR CT 40.** The dose may be increased, if necessary, to two tablets of **CRESAR CT 40** or one tablet of **CRESAR CT 80** daily.

A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg may be switched to two tablets of **CRESAR CT 40** or one tablet of **CRESAR CT 80** daily.

A patient whose blood pressure is not adequately controlled with chlorthalidone 25 mg once daily

may be switched to **CRESAR CT 40** once / twice daily or **CRESAR CT 80** once daily. Patients controlled by 25 mg chlorthalidone but who experience dose-limiting adverse reaction (such as hypokalemia) may be switched to **CRESAR CT 40** or **CRESAR CT 80** once daily, which will reduce the dose of chlorthalidone without reducing the overall expected antihypertensive response. If blood pressure remains uncontrolled after 2-4 weeks of therapy, other anti-hypertensive agents may be added as required.

Patients titrated to the individual components (telmisartan and chlorthalidone) may instead receive the corresponding dose of **CRESAR CT**.

CRESAR CT 40 may be used as initial therapy if a patient is likely to need multiple drugs to achieve blood pressure goals.

The maximum recommended daily dose of telmisartan is 80 mg and chlorthalidone is 50 mg. This means that a maximum number of tablets taken per day should not exceed two tablets of **CRESAR CT 40** and one tablet of **CRESAR CT 80**.

CRESAR CT 40/80 may be administered with other antihypertensive agents as needed. It may be administered with or without food.

Any volume depletion prior to administration of **CRESAR CT** should be corrected, particularly in patients with impaired renal function or those treated with high doses of diuretics.

Contraindications

- Known hypersensitivity (e.g. anaphylaxis or angioedema) to telmisartan, chlorthalidone or any sulfonamide-derived drugs or any other component of this product
- Anuria
- The concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (Glomerular Filtration Rate [GFR] < 60 ml/min/1.73 m^2)

Warnings and Precautions

Drug Interactions

Telmisartan

Aliskiren

Aliskiren should not be co-administered with **CRESAR CT** in patients with diabetes (due to telmisartan component). Use of aliskiren with **CRESAR CT** should also be avoided 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. Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing **CRESAR CT** for the purpose of keeping the digoxin level within the therapeutic range.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use with **CRESAR CT**.

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 **CRESAR CT** and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including **CRESAR CT** may be attenuated by NSAIDs including selective COX-2 inhibitors.

Chlorthalidone

Anti-diabetic Agents

Adjust the dosage of insulin and oral anti-diabetic agents.

Anticholinergic Agents

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and stomach-emptying rate.

Calcium Salts and Vitamin D

The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics. The resultant hypercalcemia is usually transient but may be persistent and symptomatic (weakness, fatigue, anorexia) in patients with hyperparathyroidism.

Cyclosporin

Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout-type complications.

Lithium

Thiazide and related diuretics can cause a rapid rise in serum lithium levels as the renal clearance of lithium is reduced by these compounds. Therefore, monitor serum lithium levels during concomitant use with **CRESAR CT**.

Non-Steroidal Anti-Inflammatory Agents

Concomitant administration of certain NSAIDs (e.g. indometacin) may reduce the diuretic and antihypertensive activity of chlortalidone; there have been isolated reports of a deterioration in renal function in predisposed patients.

Others

Diuretics potentiate the action of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE inhibitors).

Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as colestyramine. A decrease in the pharmacological effect may be expected.

The hypokalemic effect of diuretics may be potentiated by corticosteroids, adrenocorticotropic hormone, ß2 agonists, amphotericin and carbenoxolone.

Thiazide-induced hypokalemia or hypomagnesemia may favor the occurrence of digitalis-induced cardiac arrhythmias.

Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as colestyramine. A decrease in the pharmacological effect may be expected.

Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Hypotension

In patients with an activated renin angiotensin system (RAS), such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with telmisartan. This condition should either be corrected prior to administration of **CRESAR CT**, or treatment should be started 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.

Serum Electrolyte Imbalances

Telmisartan

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be considered, particularly in patients at risk.

Chlorthalidone

Treatment with thiazide diuretics has been associated with electrolyte disturbances such as hypokalemia, hypomagnesemia, hyperglycemia and hyponatraemia. Since the excretion of electrolytes is increased, a very strict low-salt diet should be avoided.

Hypokalaemia can sensitise the heart or exaggerate its response to the toxic effects of digitalis.

Like all thiazide diuretics, kaluresis induced by chlorthalidone is dose dependent and varies in extent from one subject to another. If necessary, **CRESAR CT** may be combined with oral potassium

supplements or a potassium-sparing diuretic (eg triamterene).

If hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis and electrocardiography alteration), **CRESAR CT** should be discontinued.

Combined treatment consisting of chlorthalidone and a potassium salt or a potassium-sparing diuretic should be avoided in patients also receiving ACE inhibitors.

Monitoring of serum electrolytes is particularly indicated in the elderly, in patients with ascites due to liver cirrhosis, and in patients with edema due to nephrotic syndrome. There have been isolated reports of hyponatremia with neurological symptoms (e.g. nausea, debility, progressive disorientation and apathy) following thiazide treatment.

For nephrotic syndrome, **CRESAR CT** should be used only under close control in normokalemic patients with no signs of volume depletion.

Dual Blockade of the RAS

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, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of **CRESAR CT** and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on **CRESAR CT** and other agents that affect the RAS.

Do not co-administer aliskiren with **CRESAR CT** (due to telmisartan component) in patients with diabetes. Avoid concomitant use of aliskiren with **CRESAR CT** (due to telmisartan component) in patients with renal impairment (GFR <60 mL/min/1.73 m2).

Metabolic Effects

Chlorthalidone may raise the serum uric acid level, but attacks of gout are uncommon during chronic treatment.

As with the use of other thiazide diuretics, glucose intolerance may occur; this is manifest as hyperglycemia and glycosuria. Chlorthalidone may very seldom aggravate or precipitate diabetes mellitus; this is usually reversible on stopping therapy.

Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for debate.

Chlorthalidone should not be used as a first-line drug for long-term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolemia (diet or combined).

As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

Others

The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.

Renal Impairment

As a consequence of inhibiting the RAS, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the RAS (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with ACE inhibitors and ARBs has been associated with oliguria and/or progressive azotemia and, rarely, with acute renal failure and/or death. Similar results have been reported with telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) were observed. There has been no long-term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Chlorthalidone should be used with caution in patients with severe renal disease. Thiazides may precipitate azotaemia in such patients, and the effects of repeated administration may be cumulative.

Hepatic Impairment

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. Monitor carefully and uptitrate telmisartan slowly in patients with biliary obstructive disorders or hepatic insufficiency.

Chlorthalidone should be used with caution in patients with impaired hepatic function or progressive liver disease since minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma, especially in patients with liver cirrhosis.

Pregnancy

Telmisartan

Risk Summary

Telmisartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the RAS during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the RAS from other antihypertensive agents. Studies in rats and rabbits with telmisartan showed fetotoxicity only at maternally toxic doses. When pregnancy is detected, discontinue telmisartan as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In

the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Disease-associated Maternal and/or Embryo/fetal Risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Use of drugs that act on the RAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. 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.

In patients taking telmisartan during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue telmisartan, unless it is considered lifesaving for the mother. 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 telmisartan for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occurs, support 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.

Data

Animal Data

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, embryo lethality 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 a mg/m2 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/m2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. 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 a mg/m2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

Chlorthalidone

Diuretics are best avoided for the management of edema or hypertension in pregnancy as their use may be associated with hypovolemia, increased blood viscosity and reduced placental perfusion. There have been reports of fetal bone marrow depression, thrombocytopenia, and fetal and neonatal jaundice associated with the use of thiazide diuretics.

Lactation

There is no information regarding the presence of telmisartan in human milk, the effects on the breastfed infant, or the effects on milk production. Telmisartan is present in the milk of lactating rats. Telmisartan was present in the milk of lactating rats at concentrations 1.5 to 2 times those found in plasma from 4 to 8 hours after administration. Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with telmisartan.

Chlorthalidone passes into the breast milk; mothers taking the drug should refrain from breast-feeding their infants.

Pediatric Use

The safety and effectiveness of telmisartan in pediatric patients have not been established.

Neonates with a History of In-utero Exposure to Telmisartan

If oliguria or hypotension occurs, attention should be directed towards 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.

Geriatric Use

Telmisartan

Of the total number of patients receiving telmisartan in hypertension clinical studies, 19% were 65 to 74 years of age and 4% were 75 years or older. 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.

Of the total number of patients receiving telmisartan in the cardiovascular risk reduction study (ONTARGET), the percentage of patients ≥65 to <75 years of age was 42%; 15% of patients were ≥75 years old. 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.

No overall differences in effectiveness and safety of telmisartan and chlorthalidone were observed in elderly patients compared to younger patients. However, greater sensitivity of some older individuals cannot be ruled out. In elderly patients, the elimination of chlorthalidone is slower than in healthy young adults, although absorption is the same. Therefore, a reduction in the recommended adult dosage may be needed. Close medical observation is indicated when treating patients of advanced age with **CRESAR CT**.

Chlorthalidone

In elderly patients, the elimination of chlorthalidone is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlorthalidone.

Undesirable Effects

Telmisartan

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Telmisartan has been evaluated for safety in more than 3700 hypertension patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20 to 160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo.

Adverse events occurring at an incidence of ≥1% in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

Table 1: Adverse events occurring at an incidence of ≥1% in patients treated with telmisartan at a greater rate than patients treated with placebo

	Telmisartan n=1455 %	**Placebo n=380 %**
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to these adverse events, the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of patients treated with telmisartan and 6.1% of patients treated with placebo, in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are listed below. It cannot be

determined whether these events were causally related to telmisartan:

Autonomic Nervous System: impotence, increased sweating, flushing

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

Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal echocardiography (ECG)

Central Nervous System: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia

Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders

Metabolic: gout, hypercholesterolemia, diabetes mellitus

Musculoskeletal: arthritis, arthralgia, leg cramps

Psychiatric: anxiety, depression, nervousness

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

Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis

Skin: dermatitis, rash, eczema, pruritus

Urinary: micturition frequency, cystitis

Vascular: cerebrovascular disorder

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

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy because of anemia.

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

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

Post-marketing Experience

The most frequent spontaneously reported events during post-approval use of telmisartan 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 (creatine phosphokinase), 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 ARBs, including telmisartan.

Chlorthalidone

Frequency estimate: very rare <0.01%, rare ≤0.01% to ≤0.1%; uncommon ≤0.1% to <1%; common ≤1% to <10%; very common ≥10%.

Electrolytes and metabolic disorders

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and rise in blood lipids.

Common: hyponatraemia, hypomagnesaemia and hyperglycaemia.

Uncommon: gout.

Rare: hypercalcaemia, glycosuria, worsening of diabetic metabolic state.

Very rare: hypochloraemic alkalosis.

Skin

Common: urticaria and other forms of skin rash.

Rare: photosensitisation.

Liver

Rare: intrahepatic cholestasis or jaundice.

Cardiovascular system

Common: postural hypotension.

Rare: cardiac arrhythmias.

Central nervous system

Common: Dizziness.

Rare: paraesthesia, headache.

Gastro-intestinal tract:

Common: loss of appetite and minor gastrointestinal distress.

Rare: mild nausea and vomiting, gastric pain, constipation and diarrhoea.

Very rare: pancreatitis.

Blood

Rare: Thrombocytopenia, leucopenia, agranulocytosis and eosinophilia.

Other effects

Common: impotence

Rare: Idiosyncratic pulmonary edema (respiratory disorders), allergic interstitial nephritis

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

Telmisartan

Limited data are available related to overdosage in humans. The most likely manifestation of overdosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Chlorthalidone

Signs and Symptoms

In poisoning due to an overdosage the following signs and symptoms may occur: dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment

There is no specific antidote to chlorthalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated.

Incompatibility

Not applicable.

Shelf-Life

2 years.

Storage and Handling Instructions

Store in a cool, dry place away from light.

Packaging Information

CRESAR CT 40: Strip of 10 tablets

CRESAR CT 80: Strip of 10 tablets

Last Updated: *Feb 2018*

Last Reviewed: *Feb 2018*