OLMESARTAN + AMLODIPINE + HYDROCHLOROTHIAZIDE

TRI-ALZOR®

20mg / 5mg / 12.5mg Film Coated Tablet
40mg / 5mg / 12.5mg Film Coated Tablet
40mg / 10mg / 12.5mg Film Coated Tablet
ANGIOTENSIN II RECEPTOR BLOCKER/
CALCIUM CHANNEL BLOCKER/ DIURETIC/
ANTI-HYPERTENSIVE

FORMULATION
Each film coated tablet contains:
Olmesartan (as medoxomil), USP.....20 mg
Amlodipine (as besilate), BP.....5 mg
Hydrochlorothiazide, BP.....12.5 mg
Each film coated tablet contains:
Olmesartan (as medoxomil) .....40 mg
Amlodipine (as besilate), BP.....5 mg
Hydrochlorothiazide, BP.....12.5 mg
Each film coated tablet contains:
Olmesartan (as medoxomil) .....40 mg
Amlodipine (as besilate), BP.....10 mg
Hydrochlorothiazide, BP.....12.5 mg

DESCRIPTION:
20mg/5mg/12.5mg: Light pink to pink coloured, circular, biconvex, film coated tablets, plain on both sides.
40mg/5mg/12.5mg: Light yellow to yellow coloured, circular, biconvex, film coated tablets, plain on both sides.
40mg/10mg/12.5mg: Light pink to pink coloured, circular, biconvex, film coated tablets, with break line on one side and plain on other side.

MECHANISM OF ACTION
The active ingredients of Tri-Alzor target three separate mechanisms involved in blood pressure regulation.

Olmesartan
Angiotensin II is formed from angiotensin I in a reaction catalysed by 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. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT1 receptor than for the AT2 receptor.

Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggests that amlodipine binds to both dihydropyridine and non-hydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

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. 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 co-administration 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.

PHARMACODYNAMICS
Combination has been shown to be effective in lowering blood pressure. The three components of Combination (olmesartan medoxomil, amlodipine, and hydrochlorothiazide) lower the blood pressure through complementary mechanisms, each working at a separate site and blocking different effects or pathways. The pharmacodynamics of each individual component is described below.

Olmesartan medoxomil
Olmesartan medoxomil doses of 2.5 to 40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of olmesartan medoxomil >40 mg giving >90% inhibition at 24 hours.

Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increase after single and repeated administration of olmesartan medoxomil to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan medoxomil had minimal influence on aldosterone levels and no effect on serum potassium.

Amlodipine
Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive patients experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Hydrochlorothiazide
After oral administration of Hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to12 hours.

PHARMACOKINETICS
The combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide
After oral administration of the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide in normal healthy adults, peak plasma concentrations of olmesartan, amlodipine and hydrochlorothiazide are reached in about 1.5 to 3 hours, 6 to 8 hours, and 1.5 to 2 hours, respectively. The rate and extent of absorption of olmesartan medoxomil, amlodipine, and hydrochlorothiazide from Tri-alzor are the same as when administered as individual dosage forms. Food does not affect the bioavailability of the combination.

Absorption
Olmesartan medoxomil
Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. The absolute bioavailability of olmesartan medoxomil is approximately 26%. After oral administration, the Cmax of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan medoxomil.

Amlodipine
After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability is estimated between 64% and 90%.

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
Olmesartan medoxomil
The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

In rats, olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan passed across the placental barrier in rats and was distributed to the fetus. Olmesartan was distributed to milk at low levels in rats.

Amlodipine
Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

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

Metabolism and Excretion
Olmesartan medoxomil
Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of he absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

Amlodipine
Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Ten percent of the parent compound and 60% of the metabolites are excreted in the urine.

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

INDICATIONS
Tri-Alzor is a combination of an angiotensin II receptor blocker, a dihydropyridine calcium channel blocker, and a thiazide diuretic indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
Tri-Alzor is not indicated for initial therapy.

CONTRAINDICATIONS
- Because of the hydrochlorothiazide component, Tri-Alzor is contraindicated in patients with anuria.
- Hypersensitivity to any component, or hypersensitivity to other sulfonamide-derived drugs.
- Do not co-administer aliskiren with Tri-Alzor in patients with diabetes.

DOSAGE AND ADMINISTRATION
Posology
- Dosage may be increased in 2 week intervals, as needed. The maximum recommended dose of combination (olmesartan medoxomil, amlodipine and hydrochlorothiazide) is 40/10/25 mg. Dose once daily. Do not crush the tablet. Or as prescribed by the physician.
- Dose selection should be individualized based on previous therapy.

Pediatric patients
The safety and effectiveness of the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide in pediatric patients have not been established.

Elderly Patients
Caution, including more frequent monitoring of blood pressure, is recommended in elderly people.

An increase of the dosage should take place with care in elderly people.

Hepatic impairment
The combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide should be used with caution in patients with mild hepatic impairment.

In patients with moderate hepatic impairment the maximum dose should not exceed Tri-Alzor 20 mg/5 mg/12.5 mg once daily. Close monitoring of blood pressure and renal function is advised in patients with hepatic impairment.

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. Tri-Alzor should therefore be administered with caution in these patients. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with impaired liver function.

Use of Tri-Alzor is contraindicated in patients with severe hepatic impairment, cholestasis or biliary obstruction.

Renal Impairment
There are no studies of the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide in patients with renal impairment. Avoid use in patients with severe renal impairment (creatinine clearance < 30 mL/min).

Method of administration:
The tablet should be swallowed with a sufficient amount of fluid (e. g. one glass of water). The tablet should not be chewed and should be taken at the same time each day.

Tri-Alzor can be taken with or without food.

WARNINGS AND PRECAUTIONS
Fetal Toxicity
Pregnancy Category D
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 the combination of olmesartan, amlodipine and hydrochlorothiazide as soon as possible.

Hypotension in Volume- or Salt-Depleted Patients
Olmesartan medoxomil
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics) symptomatic hypotension may be anticipated after initiation of treatment with olmesartan medoxomil. Initiate treatment with the combination of olmesartan, amlodipine and hydrochlorothiazide under close medical supervision. If hypotension does occur, place the patient in the supine position and, if necessary, give 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.

Amlodipine
Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Increased Angina and/or Myocardial Infarction
Amlodipine
Patients, particularly those with severe obstructive coronary artery disease, may develop increased frequency, duration, or severity of angina or acute myocardial infarction upon starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Impaired Renal Function
Impaired renal function was reported in 2.1% of subjects receiving the combination of olmesartan, amlodipine and hydrochlorothiazide compared to 0.2% to 1.3% of subjects receiving dual combination therapy of olmesartan medoxomil and amlodipine, olmesartan medoxomil and hydrochlorothiazide or amlodipine and hydrochlorothiazide.
If progressive renal impairment becomes evident consider withholding or discontinuing the combination.

Olmesartan medoxomil
Changes in renal function occur in some individuals treated with olmesartan medoxomil as a consequence of inhibiting the renin-angiotensin-aldosterone system. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure and/or death. Similar effects may occur in patients treated with the combination of olmesartan, amlodipine and hydrochlorothiazide due to the olmesartan medoxomil component.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar effects would be expected with this combination because of the olmesartan medoxomil component.

Hydrochlorothiazide
Thiazides may precipitate azotemia in patients with renal disease. Cumulative effects of the drug may develop in patients with impaired renal function.

Patients with Hepatic Impairment
Amlodipine
Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t1/2) is 56 hours in patients with severely impaired hepatic function, titrate slowly when administering to patients with severe hepatic impairment.

Electrolyte and Metabolic Imbalances
The combination of olmesartan, amlodipine and hydrochlorothiazide contains hydrochlorothiazide which can cause hypokalemia, hyponatremia and hypomagnesemia.

Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion.

The combination of olmesartan, amlodipine and hydrochlorothiazide also contains olmesartan, a drug that affects the RAS. Drugs that inhibit the RAS can also cause hyperkalemia.

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hyperuricemia may occur or frank gout may be precipitated in patients receiving thiazide therapy.
Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels.

Postsympathectomy Patients
The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

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

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 acute 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.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.

Sprue-like Enteropathy
Olmesartan medoxomil
Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with Olmesartan, exclude other etiologies. Consider discontinuation of the combination of olmesartan, amlodipine and hydrochlorothiazide in cases where no other etiology is identified.

DRUG INTERACTIONS
Drug Interactions with Olmesartan Medoxomil
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 olmesartan medoxomil, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving olmesartan medoxomil and NSAID therapy.

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

Dual Blockade of the Renin-Angiotensin System (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. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on this combination and other agents that affect the RAS.

Do not co-administer aliskiren with this combination in patients with diabetes. Avoid use of aliskiren with the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide in patients with renal impairment (GFR <60 ml/min).

Use with Colesevelam Hydrochloride
Concurrent administration of bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Consider administering olmesartan at least 4 hours before the colesevelam hydrochloride dose.

Lithium
Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of olmesartan or thiazide diuretics. Monitor lithium levels in patients receiving Tri-alzor and lithium.

Drug Interactions with Amlodipine
Simvastatin
Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Immunosuppressants
Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.

CYP3A Inhibitors
Co-administration of amlodipine with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers
No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

Drug Interactions with Hydrochlorothiazide
When administered concurrently the following drugs may interact with thiazide diuretics:
Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single dose 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.

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 hydrochlorothiazide tablets and nonsteroidal anti-inflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category D
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 combination 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 combination, 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 combination for hypotension, oliguria, and hyperkalemia.

Nursing Mothers
It is not known whether amlodipine or olmesartan are excreted in human milk, but thiazides appear in human milk and olmesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Neonates with a history of in utero exposure to combination:
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.

The safety and effectiveness of combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide in pediatric patients have not been established.

Geriatric Use
In a controlled clinical trial, 123 hypertensive patients treated with combination were ≥ 65 years of age and 18 patients were ≥75 years of age. No overall differences in the efficacy or safety of combination were observed in these patient populations; however, greater sensitivity of some older individuals cannot be ruled out. The recommended initial dose of amlodipine in patients ≥ 75 years of age is 2.5 mg, a dose not available with combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide.

Hepatic Impairment
There are no studies of combination in patients with hepatic insufficiency, but both amlodipine and olmesartan medoxomil show moderate increases in exposure in patients with severe hepatic impairment. The recommended initial dose of amlodipine in patients with severe hepatic impairment is 2.5 mg, a dose not available with combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide.

Amlodipine
Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{½}$) is 56 hours in patients with severely impaired hepatic function.

Olmesartan medoxomil
Increases in AUC0-∞ and peak plasma concentration (Cmax) for olmesartan were observed with moderate hepatic impairment compared to those in matched controls with an increase in AUC of about 60%.

Hydrochlorothiazide
In patients with impaired hepatic function or progressive liver disease, minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Renal Impairment
There are no studies of combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide in patients with renal impairment. Avoid use in patients with severe renal impairment (creatinine clearance <30 mL/min).

Olmesartan medoxomil
Patients with renal insufficiency have elevated serum concentrations of olmesartan compared with patients with normal renal function. After repeated dosing, AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 mL/min).
No initial dosage adjustment is recommended for patients with moderate to marked renal impairment (creatinine clearance <40 mL/min). The pharmacokinetics of olmesartan in patients undergoing hemodialysis has not been studied.

Amlodipine
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hydrochlorothiazide
Thiazide should be used with caution in patients with 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.

ADVERSE EFFECT
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction 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.
In the controlled trial of the combination of olmesartan, amlodipine & hydrochlorothiazide patients were randomized to this combination. Subjects who received triple combination therapy were treated between two and four weeks with one of the three dual combination therapies. Safety data from this study were obtained in 574 patients with hypertension who received this combination for 8 weeks.

The most common reason for discontinuation with this combination was dizziness (1%).

Dizziness was one of the most frequently reported adverse reactions with incidence of 1.4% to 3.6% in subjects continuing on dual combination therapy compared to 5.8% to 8.9% in subjects who switched to this combination.

The other most frequent adverse reactions that occurred in at least 2% of subjects are presented in the table below:

Adverse Reaction	OM40/AML10/ HCTZ25 mg (N = 574) n (%)	OM40/AML 10mg (N = 596) n (%)	OM40/HCT Z25mg (N = 580) n (%)	AML10/HCT Z25mg (N = 552) n (%)
Edema peripheral	44 (7.7)	42 (7.0)	6 (1.0)	46 (8.3)
Headache	37 (6.4)	42 (7.0)	38 (6.6)	33 (6.0)
Fatigue	24 (4.2)	34 (5.7)	31 (5.3)	36 (6.5)
Nasopharyngitis	20 (3.5)	11 (1.8)	20 (3.4)	16 (2.9)
Muscle spasms	18 (3.1)	12 (2.0)	14 (2.4)	13 (2.4)
Nausea	17 (3.0)	12 (2.0)	22 (3.8)	12 (2.2)
Upper respiratory tract infection	16 (2.8)	26 (4.4)	18 (3.1)	14 (2.5)
Diarrhea	15 (2.6)	14 (2.3)	12 (2.1)	9 (1.6)
Urinary tract infection	14 (2.4)	8 (1.3)	6 (1.0)	7 (1.3)
Joint swelling	12 (2.1)	17 (2.9)	2 (0.3)	16 (2.9)

Olmesartan medoxomil
Olmesartan medoxomil has been evaluated for safety in more than 3825 patients/subjects, including more than 3275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 treated for at least 1 year. Treatment with olmesartan medoxomil was well tolerated, with an incidence of adverse reactions similar to that seen with placebo. Adverse reactions were generally mild, transient, and without relationship to the dose of olmesartan medoxomil.

Amlodipine
Amlodipine has been evaluated for safety in more than 11,000 patients in clinical trials.

The following adverse reactions occurred in <1% but >0.1% of patients in controlled clinical trials under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert physicians to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo
Gastrointestinal: anorexia, constipation, dyspepsia*, dysphagia, diarrhea, flatulence, pancreatitis, vomiting. gingival hyperplasia.
General: allergic reaction, asthenia*, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
Musculoskeletal System: arthralgia, arthrosis, muscle cramps*, myalgia
Psychiatric: sexual dysfunction (male* and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization
Respiratory: dyspnea*, epistaxis
Skin and Appendages: angioedema, erythema multiforme, pruritus*, rash*, rash erythematous, rash maculopapular
Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus
Urinary System: micturition frequency, micturition disorder, nocturia
Autonomic Nervous System: dry mouth, sweating increased
Metabolic and Nutritional: hyperglycemia, thirst
Hemopoietic: leukopenia, purpura, thrombocytopenia
* = events that occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following adverse reactions occurred in <0.1% of patients: cardiac failure, pulse irregularity, extra systoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Hydrochlorothiazide
Other adverse reactions 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 the individual components of Tri-Alzor. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Olmesartan medoxomil
The following adverse reactions have been reported in post-marketing experience:

Body as a Whole: asthenia, angioedema, anaphylactic reactions, peripheral edema
Gastrointestinal: vomiting, diarrhea, sprue-like enteropathy.
Metabolic and Nutritional Disorders: hyperkalemia
Musculoskeletal: rhabdomyolysis
Urogenital System: acute renal failure, increased blood creatinine
Skin and Appendages: alopecia, pruritus, urticaria

Amlodipine
The following post-marketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In post-marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine. Post-marketing reporting has also revealed a possible association between extrapyramidal disorder and amlodipine.

OVERDOSE AND TREATMENT
There is no information on overdosage with the combination in humans.

Olmesartan medoxomil
Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension should occur, supportive treatment should be initiated. The dialyzability of olmesartan is unknown.

Amlodipine
Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential.
Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Hydrochlorothiazide.
The most common signs and symptoms of overdose observed in humans 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 LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, more than 1000-fold the highest recommended human dose.

CAUTION : Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORE AT TEMPERATURES NOT EXCEEDING 30° C.

KEEP OUT OF REACH OF CHILDREN

TRI-ALZOR® is a registered trademark of Ajanta Pharma Philippines, Inc.

AVAILABILITY
Olmesartan medoxomil + Amlodipine besilate + Hydrochlorothiazide (Tri-Alzor®) 20mg/5mg/12.5mg, Alu-alu blister pack of 10's, box of 30 film coated tablets
Olmesartan medoxomil + Amlodipine besilate + Hydrochlorothiazide (Tri-Alzor®) 40mg/5mg/12.5mg, Alu-alu blister pack of 10's, box of 30 film coated tablets
Olmesartan medoxomil + Amlodipine besilate + Hydrochlorothiazide (Tri-Alzor®) 40mg/10mg/12.5mg, Alu-alu blister pack of 10's, box of 30 film coated tablets

Registration No.: 20mg /5mg/ 12.5mg- DR-XY38890
Registration No.: 40mg /5mg/ 12.5mg- DR-XY40112
Registration No.: 40mg /10mg/ 12.5mg- DR-XY40113

Date of First Authorization / Renewal of the Authorization:
20mg/5mg/12.5mg - Nov. 13, 2015
40mg/5mg/12.5mg - Mar. 28, 2016
40mg/10mg/12.5mg - Feb. 18,2016

Date of Revision of Package Insert: November 08, 2021

Manufactured by: Ajanta Pharma Limited
Plot No. B-4/5/6, MIDC, Paithan, Aurangabad 431 148
Maharashtra State, India

Imported & Distributed by: ajanta pharma PHILIPPINES, INC.
Unit 1702 Phil. Axa Life Center,
#1286 Sen. Gil Puyat Ave. Cor. Tindalo St.,
Brgy. San Antonio, Makati City

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