For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

TRI-OLMETOR

(Olmesartan Medoxomil, Amlodipine Besilate and Hydrochlorothiazide Tablets)

COMPOSITION:

TRI-OLMETOR 20

Each film coated tablet contains:
Olmesartan Medoxomil I.P. 20 mg
Amlodipine Besilate I.P. equivalent to Amlodipine 5 mg
Hydrochlorothiazide I.P. 12.5 mg
Colours: Red Oxide of Iron, Yellow Oxide of Iron, Black Oxide of Iron and Titanium Dioxide I.P.

TRI-OLMETOR 40

Each film coated tablet contains:
Olmesartan Medoxomil I.P. 40 mg
Amlodipine Besilate I.P. equivalent to Amlodipine 5 mg
Hydrochlorothiazide I.P. 12.5 mg
Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue product as soon as possible

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

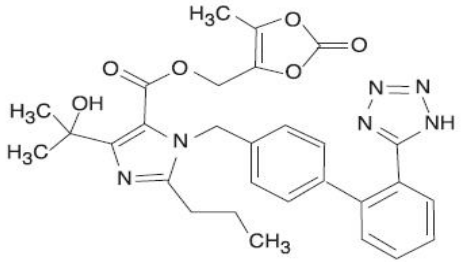
DESCRIPTION

Tri-olmetor tablet is a fixed combination of olmesartan medoxomil (ARB), amlodipine (CCB), and hydrochlorothiazide (thiazide diuretic).

Olmesartan

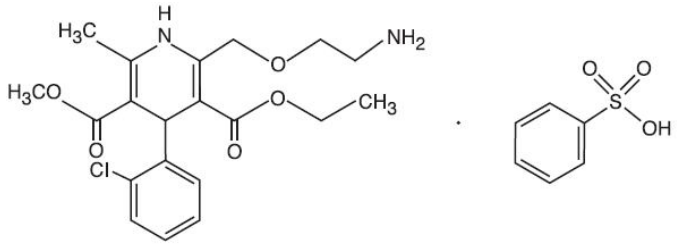
The olmesartan medoxomil component is chemically (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate. Its empirical formula is $C_{29}H_{30}N_6O_6$ and molecular weight is 558.6.

The structural formula for olmesartan medoxomil is:

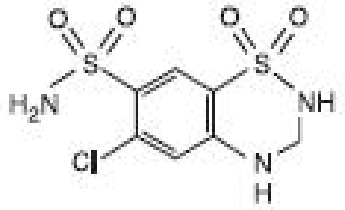


Amlodipine

The amlodipine besilate component is chemically 3-ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene sulphonate. Its empirical formula is $C_{26}H_{31}ClN_2O_8S$ and molecular weight is 567.1. The structural formula for amlodipine besilate is:



The hydrochlorothiazide component is chemically 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and molecular weight is 297.7. The structural formula for hydrochlorothiazide is:



CLINICAL PHARMACOLOGY

Pharmacodynamics:

Fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, a calcium channel blocker, amlodipine besilate and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than each component alone. Olmesartan medoxomil is an orally active, selective angiotensin II receptor (type AT_1) antagonist. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT_1 receptor in tissues including vascular smooth muscle and the adrenal gland. The action of olmesartan is independent of the source or route of synthesis of angiotensin II.

The selective antagonism of the angiotensin II (AT_1) receptors by olmesartan results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations. In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure.

There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy. Once daily dosing with olmesartan medoxomil provides an effective and smooth reduction in blood pressure over the 24 hour dose interval. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose. With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment. The effect of olmesartan medoxomil on mortality and morbidity is not yet known. The amlodipine component of fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide is a calcium channel blocker that inhibits the transmembrane influx of calcium ions through the potential-dependent L type channels into the heart and smooth muscle.

Experimental reported data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. The antihypertensive effect of amlodipine derives from a direct relaxant effect on arterial smooth muscle, which leads to a lowering of peripheral resistance and hence of blood pressure. In hypertensive patients, amlodipine causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy. Following administration of therapeutic doses to patients with hypertension, amlodipine produces an effective reduction in blood pressure in the supine, sitting and standing positions.

Chronic use of amlodipine is not associated with significant changes in heart rate or plasma catecholamine levels. In hypertensive patients with normal renal function, therapeutic doses of amlodipine reduce renal vascular resistance and increase glomerular filtration rate and effective renal plasma flow, without changing filtration fraction or proteinuria. In haemodynamic reported studies in patients with heart failure and in clinical reported studies based on exercise tests in patients with NYHA class II-IV heart failure, amlodipine was found not to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms. A placebo-controlled reported study (PRAISE) designed to evaluate patients with NYHA class III-IV heart failure receiving digitalis, diuretics and ACE inhibitors, has shown that amlodipine did not lead to an increase in the risk of mortality and morbidity in patients with heart failure. In a follow-up, long-term, placebo controlled reported study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary

potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 hours.

Epidemiological reported studies have shown that long-term treatment with hydrochlorothiazide monotherapy reduces the risk of cardiovascular mortality and morbidity.

Pharmacokinetics:
Concomitant administration of olmesartan medoxomil, amlodipine and hydrochlorothiazide had no clinically-relevant effects on the pharmacokinetics of either component in healthy subjects. Following oral administration of fixed dose 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 fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide are the same as when administered as a dual-fixed combination of olmesartan medoxomil and amlodipine together with a hydrochlorothiazide single-component tablet or when administered as a dual-fixed combination of olmesartan medoxomil and hydrochlorothiazide together with an amlodipine single-component tablet with the same dosages. Food does not affect the bioavailability of fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide.

Olmesartan:
Absorption and distribution:
Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract. No intact olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of olmesartan from a tablet formulation was 25.6%. The mean peak plasma concentration (C_{max}) of olmesartan is reached within about 2 hours after oral dosing with olmesartan medoxomil, and olmesartan\ plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg. Food had minimal effect on the bioavailability of olmesartan and therefore olmesartan medoxomil may be administered with or without food. No clinically relevant gender-related differences in the pharmacokinetics of olmesartan have been observed.

Olmesartan is highly bound to plasma protein (99.7%), but the potential for clinically significant protein binding displacement interactions between olmesartan and other highly bound co-administered active substances is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16-29 L).

Metabolism and elimination:
Total plasma clearance of olmesartan was typically 1.3 L/h (CV 19%) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of 14C-labelled olmesartan medoxomil, 10-16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6%, it can be calculated that absorbed olmesartan is cleared by both renal excretion (ca 40%) and hepato-biliary excretion (ca 60%). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated. The terminal elimination half life of olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after 2-5 days of dosing and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5-0.7 L/h and was independent of dose.

Amlodipine:
Absorption and distribution:
After oral administration of therapeutic doses, amlodipine is slowly absorbed from the gastrointestinal tract. The absorption of amlodipine is unaffected by the concomitant intake of food. The absolute bioavailability of the unchanged compound is estimated to be 64% -80%. Peak plasma levels are reached 6 to 12 hours post-dose. The volume of distribution is about 20 L/kg. The pKa of amlodipine is 8.6. Plasma protein binding in vitro is approximately 98%.

Metabolism and elimination:
The plasma elimination half-life varies from 35 to 50 hours. Steady-state plasma levels are reached after 7-8 consecutive days. Amlodipine is extensively metabolised to inactive metabolites. About 60% of the administered dose is excreted in the urine, about 10% of which in the form of unchanged amlodipine.

Hydrochlorothiazide:
Absorption and distribution:
Following oral administration of olmesartan medoxomil and hydrochlorothiazide in combination, the median time to peak concentrations of hydrochlorothiazide was 1.5 to 2 hours after dosing. Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.83 -1.14 L/kg.

Metabolism and elimination:
Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged active substance in urine. About 60% of the oral dose is eliminated as unchanged active substance within 48 hours. Renal clearance is about 250-300 mL/min. The terminal elimination half-life of hydrochlorothiazide is 10-15 hours.

Pharmacokinetics in special populations
Elderly*:*
In hypertensive patients, the olmesartan AUC at steady state was increased by ca 35% in elderly patients (65-75 years old) and by ca 44% in very elderly patients (! 75 years old) compared with

the younger age group. This may be at least in part related to a mean decrease in renal function in this group of patients. The recommended dosage regimen for elderly patients is, however, the same, although caution should be exercised when increasing the dosage. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects.

Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly patients. Increases in AUC and elimination half life in patients with congestive heart failure were reported. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly patients compared to young healthy volunteers.

Renal impairment:
In renally impaired patients, the olmesartan AUC at steady state increased by 62%, 82% and 179% in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls. The pharmacokinetics of olmesartan medoxomil in patients undergoing haemodialysis has not been reported. Amlodipine is extensively metabolised to inactive metabolites. Ten percent of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients, amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

The half-life of hydrochlorothiazide is prolonged in patients with impaired renal function.

Hepatic impairment:
After single oral administration, olmesartan AUC values are 6% and 65% higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment is 0.26%, 0.34% and 0.41%, respectively. Following repeated dosing in patients with moderate hepatic impairment, olmesartan mean AUC is again about 65% higher than in matched healthy controls.

Olmesartan mean C_{max} values are similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment. The clearance of amlodipine is decreased and the half-life is prolonged in patients with impaired hepatic function, resulting in an increase in AUC of about 40%-60%. Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide.

INDICATIONS
Treatment of essential hypertension. This fixed combination drug is not indicated for the initial therapy of hypertension

DOSAGE AND ADMINISTRATION
General Considerations Dose once daily.
Dosage may be increased after 2 weeks. The full blood pressure lowering effects are attained within 2 weeks after a change in dose. It may be taken with or without food.

Replacement Therapy
It may be substituted for its individually titrated components in patients controlled on stable doses of olmesartan medoxomil, amlodipine and hydrochlorothiazide taken at the same time.

Add-on/Switch Therapy
Fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide may be used to provide additional blood pressure lowering for patients not adequately controlled on maximally tolerated, labeled, or usual doses of any two of the following antihypertensive classes: angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and diuretics. A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide may be switched to this fixed dose combination containing a lower dose of that component to achieve similar blood pressure reductions.

Elderly (age 65 years or over)
Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients. Very limited data are available on the use of this fixed dose combination in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended.

Renal impairment
The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 30 - 60 mL/min) is fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide 20 mg/5 mg/12.5 mg, owing to limited experience of the 40 mg olmesartan medoxomil dosage in this patient group.Monitoring of serum concentrations of potassium and creatinine is advised in patients with moderate renal impairment. The use of fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide in patients with severe renal impairment (creatinine clearance < 30 mL/min) is contraindicated.

Hepatic impairment
Fixed dose 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 fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide 20 mg/5 mg/12.5 mg once daily. Close monitoring of blood pressure and renal function is advised in patients with hepatic impairment. Fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide should not be used in patients with severe hepatic impairment, cholestasis or biliary obstruction.

Paediatric population
Fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

CONTRAINDICATIONS

Do not co-administer aliskiren with Olmesartan in patients with diabetes.

Hypersensitivity to the active substances, to dihydropyridine derivates or to sulfonamide-derived substances (since hydrochlorothiazide is a sulfonamide-derived drug) or to any of the excipients.
Severe renal impairment or anuria.
Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia.
Severe hepatic insufficiency, cholestasis and biliary obstructive disorders.
2^{nd} and 3^{rd} trimester of pregnancy.
Due to the amlodipine component, fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide is contraindicated in patients with:
- Shock (including cardiogenic shock).
- Severe hypotension
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

WARNINGS AND PRECAUTIONS

Olmesartan

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 Olmesartan as soon as possible.

Morbidity in Infants

Children <1 year of age must not receive Olmesartan for hypertension. Drugs that act directly on the renin-angiotensin aldosterone system (RAAS) can have effects on the development of immature kidneys.

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin aldosterone 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. Initiate treatment 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.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with Olmesartan. In patients whose renal function may depend upon the activity of the renin-angiotensinaldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting

enzyme (ACE) 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 Olmesartan.

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 in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Sprue-like Enteropathy
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 Olmesartan in cases where no other etiology is identified.

Amlodipine
Vasodilation
Since the vasodilation attributable to amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, exercise caution, as with any other peripheral vasodilator, when administering Amlodipine and Olmesartan, particularly in patients with severe aortic stenosis.

Patients with Congestive Heart Failure
Amlodipine (5–10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8–12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsening of heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Patients with Hepatic Impairment
Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t½) is 56 hours in patients with severely impaired hepatic function, exercise caution when administering Amlodipine to patients with severe hepatic impairment.

Hydrochlorothiazide
Hepatic Impairment
Thiazides 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. Monitor serum lithium levels in patients receiving lithium and hydrochlorothiazide.

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.

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 important when the patient is vomiting excessively or receiving 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.

USE IN SPECIFIC POPULATIONS
Olmesartan
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 Olmesartan 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 Olmesartan, 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 Olmesartan for hypotension, oliguria, and hyperkalemia.

Nursing Mothers
It is not known whether olmesartan is excreted in human milk, but 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 Olmesartan: 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 antihypertensive effects of Olmesartan were evaluated in one randomized, double-blind clinical study in pediatric patients 1 to 16 years of age. The pharmacokinetics of Olmesartan was evaluated in pediatric patients 1 to 16 years of age. Olmesartan was generally well tolerated in pediatric patients, and the adverse experience profile was similar to that described for adults.

Olmesartan has not been shown to be effective for hypertension in children <6 years of age.

Children <1 year of age must not receive Olmesartan for hypertension. The renin-angiotensin aldosterone system (RAAS) plays a critical role in kidney development. RAAS blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the renin- angiotensin aldosterone system (RAAS) can alter normal renal development.

Geriatric Use
Of the total number of hypertensive patients receiving Olmesartan in clinical studies, more than 20% were 65 years of age and over, while more than 5% were 75 years of age and older. No overall differences in effectiveness or safety were observed between elderly patients and 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.

Hepatic Impairment
Increases in $AUC_{0-\infty}$ and Cmax were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%. No initial dosage adjustment is recommended for patients with moderate to marked hepatic dysfunction.

Renal Impairment
Patients with renal insufficiency have elevated serum concentrations of olmesartan compared to subjects with normal renal function. After repeated dosing, the 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)

Black Patients
The antihypertensive effect of Olmesartan was smaller in black patients (usually a low-renin population), as has been seen with ACE inhibitors, beta-blockers and other angiotensin receptor blockers.

Amlodipine
No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively about 10 and 20 times the maximum recommended human dose of 10 mg amlodipine on a mg/m^2 basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg). However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestational period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
Olmesartan
Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m^2 basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan medoxomil.

Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames

(bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung) and tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Olmesartan medoxomil tested negative *in vivo* for mutations in the MutaMouse intestine and kidney and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

Amlodipine.

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of amlodipine 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose (MRHD) of amlodipine 10 mg/day. For the rat, the highest dose was, on a mg/m^2 basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.)

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of amlodipine up to 10 mg/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m^2 basis).

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, or in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations. It was also not genotoxic *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, or the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, the Mouse Lymphoma Cell (mutagenicity) assay and 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.

DRUG INTERACTIONS

Olmesartan

No significant drug interactions were reported in studies in which Olmesartan was coadministered with digoxin or warfarin in healthy volunteers.

The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [$Al(OH)_3/Mg(OH)_2$].

Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected.

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 Valsartan and other agents that affect the RAS.

Do not co-administer aliskiren with Olmesartan in patients with diabetes. Avoid use of aliskiren with Olmesartan in patients with renal impairment (GFR <60 ml/min).

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 during concomitant administration of lithium with angiotensin II receptor antagonists, including Olmesartan. Monitor serum lithium levels during concomitant use.

Amlodipine

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of Other Agents on Amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Antacid: Co-administration of the antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Effect of Amlodipine on Other Agents Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

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 percent, 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, Non depolarizing (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. Monitor serum lithium levels during concomitant use. Refer to the package insert for lithium preparations before use of such preparation with olmesartan medoxomil-hydrochlorothiazide.

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

ADVERSE REACTIONS

The most commonly reported adverse reactions during treatment with fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide are peripheral oedema, headache and dizziness.

The following terminologies have been used in order to classify the occurrence of undesirable effects: Very common (≥ 1/10) Common (≥ 1/100 to <1/10) Uncommon (≥ 1/1,000 to <1/100) Rare (≥ 1/10,000 to <1/1,000) Very rare (<1/10,000), not known (cannot be estimated from the available data)

Table 1: Overview of adverse reactions with fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide and the single components

System Organ Class	Adverse reactions	Frequency			
		Triple drug combination (OAH*)	Olmesartan medoxomil	Amlodipine	HCTZ (hydrochloro-thiazide)
Infections and infestations	Upper respiratory tract infection	Common			
	Nasopharyngitis	Common			
	Urinary tract infection	Common	Common		
	Sialadenitis				Rare
Blood and lymphatic system disorders	Leucopenia			Very rare	Rare
	Thrombocytopenia		Uncommon	Very rare	Rare
	Bone marrow depression				Rare
	Neutropenia/Agranulocytosis				Rare
	Haemolytic anaemia				Rare
	Aplastic anaemia				Rare
Immune system disorders	Anaphylactic reaction		Uncommon		
	Drug hypersensitivity			Very rare	
Metabolism and nutrition disorders	Hyperkalaemia	Uncommon	Rare		
	Hypokalaemia	Uncommon			Common
	Anorexia				Uncommon
	Glycosuria				Common
	Hypercalcaemia				Common
	Hyperglycaemia			Very rare	Common
	Hypomagnesaemia				Common
	Hyponatriaemia				Common
	Hypochloraemia				Common
	Hypertriglyceridaemia		Common		Very common
	Hypercolesterinaemia				Very common
	Hyperuricaemia		Common		Very common
	Hypochloraemic alkalosis				Very rare
	Hyperamylasaemia				Common
Psychiatric disorders	Confusional state			Rare	Common
	Depression			Uncommon	Rare
	Apathy				Rare
	Irritability			Uncommon	
	Restlessness				Rare
	Mood changes (including anxiety)			Uncommon	
	Sleep disorders (including insomnia)			Uncommon	Rare

Nervous system disorders	Dizziness	Common	Common	Common	Common
	Headache	Common	Common	Common	Rare
	Postural dizziness	Uncommon			
	Presyncope	Uncommon			
	Dysgeusia			Uncommon	
	Hypertonia			Very rare	
	Hypoaesthesia			Uncommon	
	Paraesthesia			Uncommon	Rare
	Peripheral neuropathy			Very rare	
	Somnolence			Common	
	Syncope			Uncommon	
	Convulsions				Rare
	Loss of appetite				Uncommon
	Tremor			Uncommon	
Eye disorders	Visual disturbance (including diplopia, blurred vision)			Uncommon	Rare
	Lacrimation decreased				Rare
	Worsening of myopia				Uncommon
	Xanthopsia				Rare
Ear and labyrinth disorders	Vertigo	Uncommon	Uncommon		Rare
	Tinnitus			Uncommon	
Cardiac disorders	Palpitations	Common		Uncommon	
	Tachycardia	Uncommon			
	Myocardial infarction			Very rare	
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)			Very rare	Rare
	Angina pectoris		Uncommon	Uncommon	
Vascular disorders	Hypotension	Common	Rare	Uncommon	
	Flushing	Uncommon		Common	
	Orthostatic hypotension				Uncommon
	Vasculitis (including necrotising angiitis)			Very rare	Rare
	Thrombosis				Rare
	Embolism				Rare
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Common	Very rare	
	Bronchitis		Common		
	Dyspnoea			Uncommon	Rare
	Pharyngitis		Common		
	Rhinitis		Common	Uncommon	
	Acute interstitial pneumonia				Rare
	Respiratory distress				Uncommon
	Pulmonary oedema				Rare
Gastrointestinal disorders	Diarrhoea	Common	Common		Common
	Nausea	Common	Common	Common	Common

	Constipation	Common			Common
	Dry mouth	Uncommon		Uncommon	
	Abdominal pain		Common	Common	Common
	Altered bowel habits (including diarrhoea and constipation)			Uncommon	
	Meteorism				Common
	Dyspepsia		Common	Uncommon	
	Gastritis			Very rare	
	Gastric irritation				Common
	Gastroenteritis		Common		
	Gingival hyperplasia			Very rare	
	Paralytic ileus				Very rare
	Pancreatitis			Very rare	Rare
	Vomiting		Uncommon	Uncommon	Common
Hepato-biliary disorders	Hepatitis			Very rare	
	Jaundice (intrahepatic cholestatic icterus)			Very rare	Rare
	Acute cholecystitis				Rare
Skin and subcutaneous tissue disorders	Alopecia			Uncommon	
	Angioedema		Rare	Very rare	
	Allergic dermatitis		Uncommon		
	Erythema multiforme			Very rare	
	Erythema				Uncommon
	Cutaneous lupus erythematodes- like reactions				Rare
	Exanthema		Uncommon	Uncommon	
	Exfoliative dermatitis			Very rare	
	Hyperhydrosis			Uncommon	
	Photosensitivity reactions			Very rare	Uncommon
	Pruritus		Uncommon	Uncommon	Uncommon
	Purpura			Uncommon	Uncommon
	Quincke oedema			Very rare	
	Rash		Uncommon	Uncommon	Uncommon
	Reactivation of cutaneous lupus erythematodes				Rare
	Toxic epidermal necrolysis				Rare
	Skin discoloration			Uncommon	
	Stevens-Johnson syndrome			Very rare	
	Urticaria		Uncommon	Very rare	Uncommon

Musculoskeletal and connective tissue disorders	Muscle spasm	Common	Rare	Uncommon	
	Joint swelling	Common			
	Muscular weakness	Uncommon			Rare
	Ankle swelling			Common	
	Arthralgia			Uncommon	
	Arthritis		Common		
	Back pain		Common	Uncommon	
	Paresis				Rare
	Myalgia		Uncommon	Uncommon	
	Skeletal pain		Common		
Renal and urinary disorders	Pollakiuria	Common		Uncommon	
	Acute renal failure		Rare		
	Haematuria		Common		
	Micturition disorder			Uncommon	
	Nocturia			Uncommon	
	Interstitial nephritis				Rare
	Renal insufficiency		Rare		Rare
Reproductive system and breast disorders	Erectile dysfunction	Uncommon		Uncommon	Uncommon
	Gynaecomastia			Uncommon	
General disorders and administration site conditions	Asthenia	Common	Uncommon	Uncommon	
	Peripheral oedema	Common	Common		
	Fatigue	Common	Common	Common	
	Chest pain		Common	Uncommon	
	Fever				Rare
	Influenza-like symptoms		Common		
	Lethargy		Rare		
	Malaise		Uncommon	Uncommon	
	Oedema			Common	
	Pain		Common	Uncommon	
	Face oedema		Uncommon		
Investigations	Blood creatinine increased	Common	Rare		Common
	Blood urea increased	Common	Common		Common
	Blood uric acid increased	Common			
	Blood potassium decreased	Uncommon			
	Gamma glytamyl transferase increased	Uncommon			
	Alanine aminotransferase increased	Uncommon			
	Aspartate aminotransferase increased	Uncommon			
	Hepatic enzymes increased		Common	Very rare (mostly consistent with cholestatis)	
	Blood creatine phosphokinase increased		Common		
	Weight decrease			Uncommon	
	Weight increase			Uncommon	

*OAH: Fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide.
Single cases of rhabdomyolysis have been reported in temporal association with the intake of angiotensin II receptor blockers.

Further adverse reactions reported that or from post marketing experience with a fixed-dose combination of olmesartan medoxomil and amlodipine and not already reported for fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, olmesartan medoxomil monotherapy or amlodipine monotherapy or reported in a higher frequency for the dual combination (Table 2):

Table 2: Combination of olmesartan medoxomil and amlodipine		
System Organ Class	**Frequency**	**Adverse reactions**
Immune system disorders	Rare	Drug hypersensitivity
Gastrointestinal disorders	Uncommon	Upper abdominal pain
Reproductive system and breast disorders	Uncommon	Libido decreased
General disorders and administration site conditions	Common	Pitting oedema
	Uncommon	Lethargy

Olmesartan medoxomil monotherapy or hydrochlorothiazide monotherapy or reported in a higher frequency for the dual combination (Table 3):

Table 3: Combination of olmesartan medoxomil and hydrochlorothiazide		
System Organ Class	**Frequency**	**Adverse reactions**
Nervous system disorders	Rare	Disturbancesin consciousness (such as loss of consciousness)
Skin and subcutaneous tissue disorders	Uncommon	Eczema
Musculosceletal and connective tissue disorders	Uncommon	Pain in extremity
Investigations	Rare	Minor decreases in mean haemoglobin and haematocrit values

Post-Marketing Experience
The following adverse reactions have been reported in post-marketing experience. 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.
Body as a Whole: Asthenia, angioedema, anaphylactic reactions

Gastrointestinal: Vomiting, sprue-like enteropathy

Metabolic and Nutritional Disorders: Hyperkalemia

Musculoskeletal: Rhabdomyolysis

Urogenital System: Acute renal failure, increased blood creatinine levels

Skin and Appendages: Alopecia, pruritus, urticarial

Data from one controlled trial and an epidemiologic study have suggested that high-dose olmesartan may increase cardiovascular (CV) risk in diabetic patients, but the overall data are not conclusive. The randomized, placebo-controlled, double-blind ROADMAP trial (Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention trial, n=4447) examined the use of olmesartan, 40 mg daily, vs. placebo in patients with type 2 diabetes mellitus, normoalbuminuria, and at least one additional risk factor for CV disease. The trial met its primary endpoint, decrease in time-to-onset of microalbuminuria, but olmesartan had no beneficial effect on decline in glomerular filtration rate (GFR). There was a finding of increased CV mortality (adjudicated sudden cardiac death, fatal myocardial infarction, fatal stroke, revascularization death) in the olmesartan group compared to the placebo group (15 olmesartan vs. 3 placebo, HR 4.9, 95% confidence interval [CI], 1.4, 17), but the risk of non-fatal myocardial infarction was lower with olmesartan (HR 0.64, 95% CI 0.35, 1.18).

The epidemiologic study included patients 65 years and older with overall exposure of > 300,000 patient-years. In the sub-group of diabetic patients receiving high-dose olmesartan (40 mg/d) for > 6 months, there appeared to be an increased risk of death (HR 2.0, 95% CI 1.1, 3.8) compared to similar patients taking other angiotensin receptor blockers. In contrast, high-dose olmesartan use in non-diabetic patients appeared to be associated with a decreased risk of death (HR 0.46, 95% CI 0.24, 0.86) compared to similar patients taking other angiotensin receptor blockers. No differences were observed between the groups receiving lower doses of olmesartan compared to other angiotensin blockers or those receiving therapy for < 6 months.

Overall, these data raise a concern of a possible increased CV risk associated with the use of high-dose olmesartan in diabetic patients. There are, however, concerns with the credibility of the finding of increased CV risk, notably the observation in the large epidemiologic study for a survival benefit in non-diabetics of a magnitude similar to the adverse finding in diabetics.

OVERDOSAGE

Symptoms:

The maximum dose of fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide is 40 mg/10 mg/25 mg once daily. There is no information on overdosage with fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide in humans. The most likely effect of fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide overdosage is hypotension. The most likely effects of olmesartan medoxomil overdosage are hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurred. Amlodipine overdosage can be expected to lead to excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension, up to and including shock with fatal outcome, has been reported. Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment:
In the event of overdosage with fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, treatment should be symptomatic and supportive. Management depends upon the time since ingestion and the severity of the symptoms. If intake is recent, gastric lavage may be considered. In healthy subjects, the administration of activated charcoal immediately or up to 2 hours after ingestion of amlodipine has been shown to reduce substantially the absorption of amlodipine. Clinically significant hypotension due to an overdose of fixed dose combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide requires active support of the cardiovascular system, including close monitoring of heart and lung function, elevation of the extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit. The dialysability of olmesartan or hydrochlorothiazide is unknown. The degree to which olmesartan and hydrochlorothiazide are removed by haemodialysis has not been established.

PRESENTATION:
TRI-OLMETOR 20 and TRI-OLMETOR 40 are available as strip of 10 tablets.

EXPIRY DATE:
Do not use later than the date of expiry.

STORAGE:
Store at a temperature not exceeding 30^{o}C, protected from light and moisture.
Keep out of reach of children.

MARKETED BY

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IN/TRIOLMETOR 20,40mg/MAR-16/05/PI