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

OLMETOR AM
(Olmesartan Medoxomil and Amlodipine Besilate Tablets)

COMPOSITION

Each film coated tablet contains:
Olmesartan Medoxomil Ph. Eur……. 20 mg
Amlodipine Besilate I.P.
Equivalent to Amlodipine……. 5 mg
Color: Titanium Dioxide I.P.

Each film coated tablet contains:
Olmesartan Medoxomil Ph.Eur…….. 40 mg
Amlodipine Besilate I.P.
Equivalent to Amlodipine……. 5 mg
Color: Yellow Oxide of Iron and Titanium Dioxide I.P.

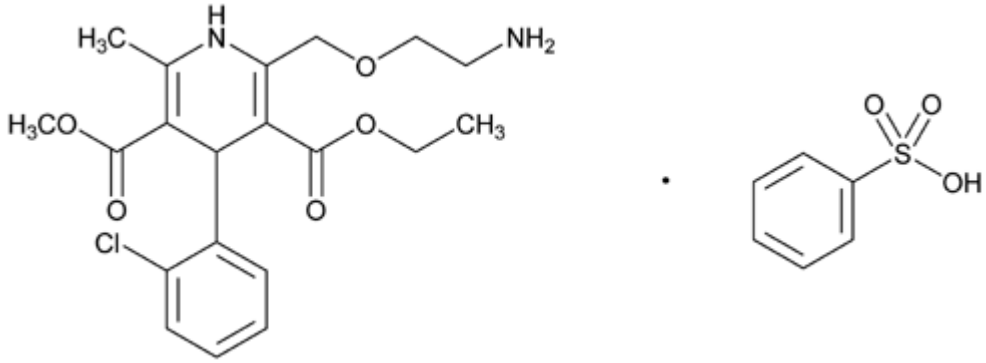
WARNING: FETAL TOXICITY
When pregnancy is detected, discontinue product as soon as possible
Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

DESCRIPTION

Olmetor AM provided as a tablet for oral administration, is a combination of the calcium channel blocker (CCB) amlodipine besylate and the angiotensin II receptor blocker (ARB) olmesartan medoxomil.

The amlodipine besylate is chemically described as 3-ethyl-5- methyl (±)-2- [(2-aminoethoxy)methyl] -4- (2-chlorophenyl)-1,4- dihydro-6- methyl-3,5- pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

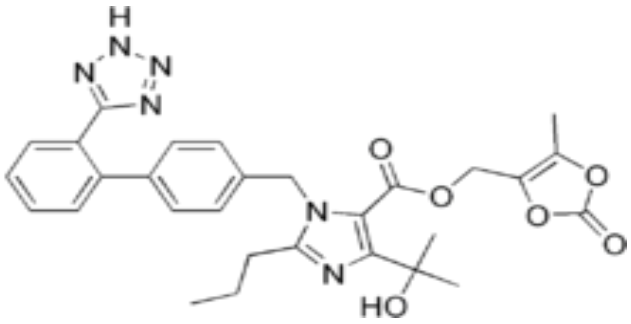
The structural formula for amlodipine besylate is:



Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract.

The olmesartan medoxomil is chemically described as 2,3- dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5- ylphenyl) benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is C29H30N6O6.

The structural formula for olmesartan medoxomil is:



Olmetor AM contains amlodipine besylate, a white to off-white crystalline powder, and olmesartan medoxomil, a white to light yellowish-white powder or crystalline powder. The molecular weights of amlodipine besylate and olmesartan medoxomil are 567.1 and 558.59, respectively. Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol. Olmesartan medoxomil is practically insoluble in water and sparingly soluble in methanol.

CLINICAL PHARMACOLOGY

Mechanism of Action

Olmetor AM is a combination of two antihypertensive drugs: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker, olmesartan medoxomil. The amlodipine component of Olmetor AM inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, and the olmesartan medoxomil component of Olmetor AM blocks the vasoconstrictor effects of angiotensin II.

Amlodipine

Experimental data suggests that amlodipine binds to both dihydropyridine and nonhydropyridine 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. Negative inotropic effects can be detected *in vitro* but such effects have not been reported in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

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.

Olmesartan medoxomil
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT_2 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 AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known.

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

Pharmacodynamics
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 subjects 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.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been reported in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

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 reported.

Olmesartan medoxomil
Olmesartan medoxomil doses of 2.5 mg 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.

Pharmacokinetics
The pharmacokinetics of amlodipine and olmesartan medoxomil are equivalent to the pharmacokinetics of amlodipine and olmesartan medoxomil when administered separately. The bioavailability of both components is well below 100%, but neither component is affected by food. The effective half-lives of amlodipine (45±11 hours) and olmesartan (7±1 hours) result in a 2- to 3- fold accumulation for amlodipine and negligible accumulation for olmesartan with once-daily dosing.

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

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 peak plasma concentration (Cmax) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan medoxomil.

Distribution

Amlodipine

Ex vivo studies have reported 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.

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.

Metabolism and Excretion

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.

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 the 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 follows 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.

Geriatric

The pharmacokinetic properties of combination of Amlodipine and Olmesartan in the elderly are similar to those of the individual components.

Amlodipine

Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%, and a lower initial dose may be required.

Olmesartan medoxomil

The pharmacokinetics of olmesartan medoxomil were studied in the elderly (>65 years). Overall, maximum plasma concentrations of olmesartan were similar in young adults and the elderly. Modest accumulation of olmesartan was reported in the elderly with repeated dosing; AUCss, τ was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CLR.

Pediatric

Amlodipine

Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Olmesartan medoxomil

The pharmacokinetics of olmesartan medoxomil have not been investigated in patients <18 years of age.

Gender

Population pharmacokinetic analysis indicated that female patients had approximately 15% smaller clearances of olmesartan than male patients. Gender had no effect on the clearance of amlodipine.

Olmesartan medoxomil

Minor differences were reported in the pharmacokinetics of olmesartan medoxomil in women compared to men. AUC and Cmax were 10% to 15% higher in women than in men.

Renal Insufficiency

Amlodipine

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Olmesartan medoxomil

In patients with renal insufficiency, serum concentrations of olmesartan were elevated 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). The pharmacokinetics of olmesartan medoxomil in patients undergoing hemodialysis has not been reported. No initial dosage adjustment is recommended for patients with moderate to marked renal impairment (creatinine clearance <40 mL/min).

Hepatic Insufficiency

Amlodipine

Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%.

Olmesartan medoxomil

Increases in AUC0-∞ and Cmax were reported in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%.

Heart Failure

Amlodipine

Patients with heart failure have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%.

Drug Interaction

Bile acid sequestering agent colesevelam

Concomitant administration of 40 mg olmesartan medoxomil and 3750 mg colesevelam hydrochloride in healthy subjects resulted in 28% reduction in Cmax and 39% reduction in AUC of olmesartan. Lesser effects, 4% and 15% reduction in Cmax and AUC respectively, were reported when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride.

INDICATIONS

For the treatment of mild to moderate hypertension.

DOSAGE AND ADMINISTRATION

General Considerations

The side effects of olmesartan medoxomil are generally rare and apparently independent of dose. Those of amlodipine are generally dose-dependent (mostly edema).

Maximum antihypertensive effects are attained within 2 weeks after a change in dose.
FDC of Amlodipine and Olmesartan medoxomil may be taken with or without food.

FDC of Amlodipine and Olmesartan medoxomil may be administered with other antihypertensive agents.

Dosage may be increased after 2 weeks. The maximum recommended dose of FDC of Amlodipine and Olmesartan medoxomil is 10/40 mg.

Replacement Therapy

FDC of Amlodipine and Olmesartan medoxomil may be substituted for its individually titrated components. When substituting for individual components, the dose of one or both of the components can be increased if blood pressure control has not been satisfactory.

Add-on Therapy

FDC of Amlodipine and Olmesartan medoxomil may be used to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with olmesartan medoxomil (or another angiotensin receptor blocker) alone.

Initial Therapy

The usual starting dose of Olmetor AM is 5/20 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum dose of one 10/40 mg tablet once daily as needed to control blood pressure.
Initial therapy with Olmetor AM is not recommended in patients ≥75 years old or with hepatic impairment.

Olmetor AM has a "CHARACTERISTIC ODOUR".

CONTRAINDICATIONS

Do not co-administer aliskiren with Olmetor AM in patients with diabetes.

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 combination of Amlodipine and Olmesartan as soon as possible.

Hypotension in Volume- or Salt-Depleted Patients

Olmesartan medoxomil

Symptomatic hypotension may be anticipated after initiation of treatment with olmesartan medoxomil. 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) may be particularly vulnerable. Initiate treatment with combination of Amlodipine and Olmesartan 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.

Vasodilation

Amlodipine

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

Patients with Severe Obstructive Coronary Artery Disease

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

Patients with Congestive Heart Failure

Amlodipine

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 Impaired Renal Function
There are no studies for combination of Amlodipine and Olmesartan in patients with renal impairment.

Olmesartan medoxomil
Changes in renal function may be anticipated in susceptible 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 angiotensin converting enzyme 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 combination of Amlodipine and Olmesartan because of 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 olmesartan medoxomil and combination of Amlodipine and Olmesartan.

Patients with Hepatic Impairment
Amlodipine
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 combination of Amlodipine and Olmesartan to patients with severe hepatic impairment.

Patients with hepatic impairment have decreased clearance of amlodipine. Starting amlodipine or adding amlodipine at 2.5 mg in hepatically impaired patients is recommended. The lowest dose of Olmetor AM is 5/20 mg; therefore, initial therapy with Olmetor AM is not recommended in hepatically impaired patients.

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 Olmetor AM in cases where no other etiology is identified.

Laboratory Tests
There was a greater decrease in hemoglobin and hematocrit in the combination product compared to either component. Other laboratory changes can usually be attributed to either monotherapy component.

Amlodipine
In post-marketing experience, hepatic enzyme elevations have been reported.

Olmesartan medoxomil
In post-marketing experience, increased blood creatinine levels and hyperkalemia have been reported.

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 Olmetor AM 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 Olmetor AM, 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 Olmetor AM for hypotension, oliguria, and hyperkalemia.

Olmesartan
No teratogenic effects were reported when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1000 mg/kg/day (240 times the maximum recommended human dose (MRHD) on a mg/m2 basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m2 basis; higher doses could not be evaluated for effects on fetal development as they were lethal to the does). In rats, significant decreases in pup birth weight and weight gain were reported at doses ≥1.6 mg/kg/day, and delays in developmental milestones (delayed separation of ear auricular, eruption of lower incisors, appearance of abdominal hair, descent of testes, and separation of eyelids) and dose-dependent increases in the incidence of dilation of the renal pelvis were reported at doses ≥ 8 mg/kg/day. The no reported effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

Amlodipine
No evidence of teratogenicity or other embryo/fetal toxicity was reported 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/m2 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 reported 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.

Nursing Mothers
It is not known whether the amlodipine or olmesartan medoxomil components of Olmetor AM are 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 Olmetor AM:
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 fixed dose combination of Amlodipine and Olmesartan in pediatric patients have not been established.

Amlodipine
The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Olmesartan medoxomil
Safety and effectiveness of olmesartan medoxomil in pediatric patients have not been established.

Geriatric Use
Of the total number of subjects in the double-blind clinical study of Fixed dose combination of Amlodipine and Olmesartan, 20% (384/1940) were 65 years of age or older and 3% (62/1940) were 75 years or older. No overall differences in safety or effectiveness were reported between subjects 65 years of age or older and younger subjects.

Elderly patients have decreased clearance of amlodipine. Starting amlodipine or adding amlodipine at 2.5 mg in patient's ≥75 years old is recommended. The lowest dose of Olmetor

AM is 5/20 mg; therefore, initial therapy with Olmetor AM is not recommended in patients ≥75 years old.

Amlodipine
Reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60%, and a lower initial dose may be required.

Olmesartan medoxomil
Of the total number of hypertensive patients receiving olmesartan medoxomil 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 reported 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
There are no studies of Fixed dose combination of Amlodipine and Olmesartan in patients with hepatic insufficiency, but both amlodipine and olmesartan medoxomil show moderate increases in exposure in patients with hepatic impairment. Use caution when administering Olmetor AM to patients with severe hepatic impairment.

Patients with hepatic impairment have decreased clearance of amlodipine. Starting amlodipine or adding amlodipine at 2.5 mg in patients with hepatic impairment is recommended. The lowest dose of Olmetor AM is 5/20 mg; therefore, initial therapy with Olmetor AM is not recommended in hepatically impaired patients.

Renal Impairment
There are no studies of fixed dose combination of Amlodipine and Olmesartan in patients with renal impairment.

Amlodipine
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

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).

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 reported no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m2 basis, similar to the maximum recommended human dose (MRHD) of amlodipine 10 mg/day. For the rat, the highest dose was, on a mg/m2 basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.)

Mutagenicity studies reported 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/m2 basis).

Olmesartan medoxomil

Olmesartan 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/m2 basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies reported 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. Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and reported no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were reported 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 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.

DRUG INTERACTIONS

Drug Interactions with Fixed dose combination of Amlodipine and Olmesartan

The pharmacokinetics of amlodipine and olmesartan medoxomil is not altered when the drugs are co-administered.

No drug interaction studies have been reported with fixed dose combination of Amlodipine and Olmesartan medoxomil and other drugs, although studies have been reported with the individual amlodipine and olmesartan medoxomil components of Olmetor AM, as described below, and no significant drug interactions have been reported.

Drug Interactions with Amlodipine
In vitro data report 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.

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.

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.

No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with digoxin or warfarin in healthy volunteers.

The bioavailability of olmesartan medoxomil 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.

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 Olmesartan and other agents that affect the RAS.

Do not co-administer aliskiren with Olmetor AM in patients with diabetes. Avoid use of aliskiren with Olmetor AM 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 during concomitant administration of lithium with angiotensin II receptor antagonists, including Olmesartan. Monitor serum lithium levels during concomitant use.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates reported 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 reported in practice.

The data described below reflect exposure to Combination of Olmesartan and Amlodipine in more than 1600 patients including more than 1000 exposed for at least 6 months and more than 700 exposed for 1 year. FDC of Olmesartan and Amlodipine was studied in one placebo-controlled factorial trial. The population had a mean age of 54 years and included approximately 55% males. Seventy-one percent were Caucasian and 25% were Black. Patients received doses ranging from 5/20 mg to 10/40 mg orally once daily.

The overall incidence of adverse reactions on therapy with FDC of Olmesartan and Amlodipine was similar to that reported with corresponding doses of the individual components of FDC of Olmesartan and Amlodipine, and to placebo. The reported adverse reactions were generally mild and seldom led to discontinuation of treatment (2.6% for FDC of Olmesartan and Amlodipine and 6.8% for placebo).

Edema
Edema is a known, dose-dependent adverse effect of amlodipine but not of olmesartan medoxomil.
The placebo-subtracted incidence of edema during the 8-week, randomized, double-blind treatment period was highest with amlodipine 10 mg monotherapy. The incidence was significantly reduced when 20 mg or 40 mg of olmesartan medoxomil was added to the 10 mg amlodipine dose.

Placebo-Subtracted Incidence of Edema during the Double-Blind Treatment Period

		Olmesartan Medoxomil		
		Placebo	**20 mg**	**40 mg**
Amlodipine	**Placebo**	-*	-2.4%	6.2%
	5 mg	0.7%	5.7%	6.2%
	10 mg	24.5%	13.3%	11.2%
*12.3% = actual placebo incidence				

Across all treatment groups, the frequency of edema was generally higher in women than men, as has been reported in previous studies of amlodipine.
Adverse reactions reported at lower rates during the double-blind period also occurred in the patients treated with combination of Amlodipine and Olmesartan at about the same or greater incidence as in patients receiving placebo. These included hypotension, orthostatic hypotension, rash, pruritus, palpitation, urinary frequency, and nocturia.

The adverse event profile obtained from 44 weeks of open-label combination therapy with amlodipine plus olmesartan medoxomil was similar to that reported during the 8-week, double-blind, placebo-controlled period.

Initial Therapy
Analyzing the data described above specifically for initial therapy, it was reported that higher doses of combination of Amlodipine and Olmesartan caused slightly more hypotension and orthostatic symptoms, but not at the recommended starting dose of Fixed dose combination of Amlodipine and Olmesartan, 5/20 mg. No increase in the incidence of syncope or near syncope

was reported. The incidences of discontinuation because of any treatment emergent adverse events in the double blind phase are summarized in the table below.

Discontinuation for any Treatment Emergent Adverse Event[1]

		Olmesartan Medoxomil			
		Placebo	**10 mg**	**20 mg**	**40 mg**
Amlodipine	Placebo	4.9%	4.3%	5.6%	3.1%
	5 mg	3.7%	0.0%	1.2%	3.7%
	10 mg	5.5%	6.8%	2.5%	5.6%

[1] Hypertension is counted as treatment failure and not as treatment emergent adverseevent.
N=160-163 subjects per treatment group.

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of amlodipine- treated patients and about 1% of placebo-treated patients.

The most common side effects were headache and edema. The incidence (%) of dose-related side effects was as follows:

Adverse Event	Placebo N=520	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268
Edema	0.6	1.8	3.0	10.8
Dizziness	1.5	1.1	3.4	3.4
Flushing	0.0	0.7	1.4	2.6
Palpitation	0.6	0.7	1.4	4.5

For several adverse experiences that appear to be drug- and dose-related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

Adverse Even	Placebo		Amlodipine	
	Male=% (N=914)	Female=% (N=336)	Male=% (N=1218)	Female=% (N=512)
Edema	1.4	5.1	5.6	14.6
Flushing	0.3	0.9	1.5	4.5
Palpitation	0.9	0.9	1.4	3.3
Somnolence	0.8	0.3	1.3	1.6

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 events similar to that reported with placebo.

Events were generally mild, transient, and without relationship to the dose of olmesartan medoxomil.

The overall frequency of adverse events was not dose-related. Analysis of gender, age, and race groups demonstrated no differences between olmesartan medoxomil- and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e., 79/3278) of patients treated with olmesartan medoxomil and 2.7% (i.e., 32/1179) of control patients. In placebo-controlled trials, the only adverse event that reported in more than 1% of patients treated with olmesartan medoxomil and at a higher incidence in olmesartan medoxomil treated patients vs. placebo was dizziness (3% vs 1%).

Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of the individual components of fixed dose combination of Amlodipine and Olmesartan. 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.

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.

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

Musculoskeletal: rhabdomyolysis

Urogenital System: acute renal failure

Skin and Appendages: alopecia, pruritus, urticaria

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
There is no information on overdosage with FDC of Amlodipine and Olmesartan in humans.

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/m2basis) 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.

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.

EXPIRY DATE
Do not use later than the date of expiry

STORAGE
Store at a temperature not exceeding 30°C, protected from moisture.
Keep out of reach of children.

PRESENTATION
OLMETOR AM is available in strip pack of 10 tablets.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

OLMA/OCT 2014/Ver 05