

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

OLMETOR M

Olmesartan Medoxomil and Metoprolol Succinate (ER) Tablets

COMPOSITION:

Olmator M 25

Each film coated bilayered tablet contains:

Olmesartan Medoxomil Ph. Eur. 20 mg

Metoprolol Succinate U.S.P. 23.75 mg

Equivalent to Metoprolol Tartrate 25 mg (As extended release form)

Colour: Lake of Sunset Yellow FCF

Olmator M 50

Each film coated bilayered tablet contains:

Olmesartan Medoxomil Ph. Eur. 20 mg

Metoprolol Succinate U.S.P. 47.50 mg

Equivalent to Metoprolol Tartrate 50 mg (As extended release form)

Colour: Yellow Oxide of Iron

WARNING: FETAL TOXICITY

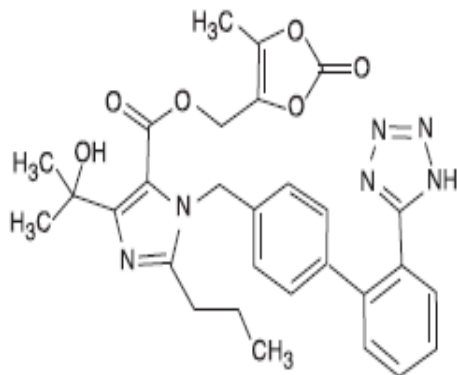
When pregnancy is detected, discontinue product as soon as possible.

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

DESCRIPTION

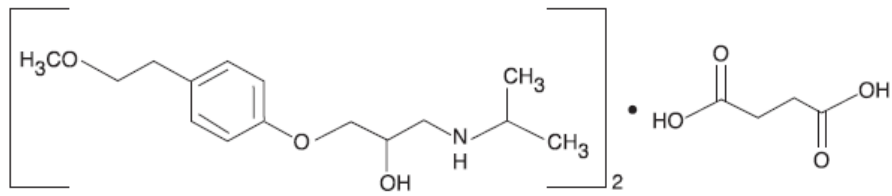
Olmesartan

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist. Olmesartan medoxomil is described chemically as (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl- (1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-imidazole 5-carboxylate. Its empirical formula is $C_{29}H_{30}N_6O_6$; molecular weight is 558.6 and structural formula is:



Metoprolol

Metoprolol is beta₁-selective adrenoceptor blocker. Its chemical name is (±)-1-(isopropyl amino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol succinate(2:1) (salt). Its empirical formula is $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$; molecular weight is 652.81 and structural formula is:



CLINICAL PHARMACOLOGY

PHARMACODYNAMIC

Olmesartan

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 AT₁ receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis. An AT₂ receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT₁ receptor than for the AT₂ receptor. 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 medoxomil 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. Olmesartan 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 >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 to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg Olmesartan had minimal influence on aldosterone levels and no effect on serum potassium.

Metoprolol:

Hypertension: The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed:

- (1) Competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output;
- (2) A central effect leading to reduced sympathetic outflow to the periphery; and
- (3) Suppression of renin activity.

Heart Failure: The precise mechanism for the beneficial effects of beta-blockers in heart failure has not been elucidated. Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as reported by

- (1) Reduction in heart rate and cardiac output at rest and upon exercise,
- (2) Reduction of systolic blood pressure upon exercise,

- (3) Inhibition of isoproterenol-induced tachycardia, and
- (4) Reduction of reflex orthostatic tachycardia. Metoprolol is a beta₁-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta₂-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction. The relative beta₁-selectivity of metoprolol has been confirmed by the following:

(1) In normal subjects, metoprolol is unable to reverse the beta₂-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine.

(2) In asthmatic patients, metoprolol reduces FEV₁ and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta₁-receptor blocking doses. The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation.

Using an E_{max} model, the maximum effect is a 30% reduction in exercise heart rate, which is attributed to beta₁-blockade.

Beta₁-blocking effects in the range of 30-80% of the maximal effect (approximately 8-23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30-540 nmol/L. The relative beta₁-selectivity of metoprolol diminishes and blockade of beta₂-adrenoreceptors increases at plasma concentration above 300 nmol/L.

Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta₂-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients. In other studies, treatment with Metoprolol succinate extended release formulation produced an improvement in left ventricular ejection fraction. Metoprolol succinate extended release formulation was also reported to delay the increase in left ventricular end-systolic and end-diastolic volumes after 6 months of treatment.

Pharmacokinetic

Olmesartan:

Absorption

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (C_{max}) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.

Distribution

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

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 shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

Geriatric

The pharmacokinetics of olmesartan was reported in the elderly (≥ 65 years). Overall, maximum plasma concentrations of olmesartan were similar in young adults and the elderly. Modest accumulation of olmesartan was observed in the elderly with repeated dosing; AUC_{ss} was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CLR.

Pediatric

The pharmacokinetics of olmesartan was reported in pediatric hypertensive patients aged 1 to 16 years. The clearance of olmesartan in pediatric patients was similar to that in adult patients when adjusted by the body weight. Olmesartan pharmacokinetics has not been investigated in pediatric patients less than 1 year of age.

Gender

Minor differences were reported in the pharmacokinetics of olmesartan in women compared to men. AUC and C_{max} were 10-15% higher in women than in men.

Hepatic Insufficiency

Increases in AUC_{0-inf} and C_{max} were reported in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%.

Renal Insufficiency

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 in patients undergoing hemodialysis has not been studied.

Drug Interactions

Bile acid sequestering agent colesevelam

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

PHARMACOKINETICS:

Metoprolol

Adults: In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin.

Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype.

Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in metoprolol succinate dosage is usually needed in patients with chronic renal failure.

Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Metoprolol succinate extended release formulation characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of Metoprolol succinate extended release formulation average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Metoprolol succinate extended release formulation, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24-hour dosing interval, Alpha-1-blockade is comparable and dose-related. The bioavailability of metoprolol reported a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Metoprolol succinate extended release formulation administration.

Pediatrics:

The pharmacokinetic profile of Metoprolol succinate extended release formulation was reported in 120 pediatric hypertensive patients (6-17 years of age) receiving doses ranging from 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol were similar to those described previously in adults. Age, gender, race, and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight. Metoprolol pharmacokinetics have not been investigated in patients < 6 years of age.

INDICATION

For the treatment of essential hypertension

Contraindication

- Do not co-administer aliskiren with Olmesartan in patients with diabetes.
- Contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and in patients who are hypersensitive to any component of this product.

DOSAGE AND ADMINISTRATION

It is once daily preparation

Tablets to be swallowed whole, not to be crushed, chewed or broken.

Adult hypertension

The therapy should be started with low dose. The dose may be increased based on clinical response of the patients on weekly (or longer) basis up to two unit of olmesartan medoxomil 20mg with metoprolol succinate 50mg once daily.

Pediatric Hypertensive Patients ≥ 6 Years of age: Olmesartan medoxomil: Maximum of 20 mg once daily for patients who weigh <35 kg or 40 mg once daily for patients who weigh ≥ 35 kg.

Metoprolol:

Maximum initial dose should not exceed 50 mg once daily. Then dose can be titrated up to two unit of olmesartan medoxomil 20mg with metoprolol succinate 50mg once daily.

Special consideration for patients with depletion of intravascular volume:

For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), initiate Olmesartan under close medical supervision and give consideration to use of a lower starting dose.

WARNINGS AND PRECASUTIONS**Olmesartan****USE IN PREGNANCY**

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Olmetor M should be discontinued as soon as possible.

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature of patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, Olmetor M should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Olmetor M as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, Olmetor M should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

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-angiotensin-aldosterone 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.

Metoprolol

Ischemic Heart Disease

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Metoprolol succinate extended release formulation, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1-2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate Metoprolol succinate extended release formulation, and take measures appropriate for the management of unstable angina.

Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing Metoprolol succinate extended release formulation in patients treated only for hypertension.

Heart Failure

Worsening cardiac failure may occur during up-titration of Metoprolol succinate extended release formulation. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of this formulation. It may be necessary to lower the dose of this formulation or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Metoprolol succinate extended release formulation.

Bronchospastic Disease

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta₁ cardio-selectivity, however, Metoprolol succinate extended release formulation may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta₁-selectivity is not absolute, use the lowest possible dose of Metoprolol succinate extended release formulation. Bronchodilators, including beta₂-agonists, should be readily available or administered concomitantly.

Pheochromocytoma

If Metoprolol succinate extended release formulation is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Major Surgery

Avoid initiation of a high-dose regimen of extended-release metoprolol in patients undergoing non-cardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia

Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Hepatic Impairment

Consider initiating Metoprolol succinate extended release formulation therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Calcium Channel Blockers

Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

USE IN SPECIAL POPULATION

Pregnancy

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.

Metoprolol

Pregnancy Category C

Metoprolol tartrate has been reported to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers

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

This formulation not recommended with the age below 6 years.

Geriatric Use

In general, use a low initial starting dose in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

Initiate therapy at doses lower than those recommended for a given indication; and increase doses gradually in patients with impaired hepatic function

Renal Impairment

Patients with renal insufficiency have elevated serum concentrations of olmesartan compared to subjects with normal renal function. However, No initial dosage adjustment is recommended for patients with moderate to marked renal impairment (creatinine clearance greater than 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

DRUG INTERACTION

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 Olmesartan 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.

Metoprolol

Catecholamine Depleting Drugs

Catecholamine depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with Metoprolol succinate extended release formulation plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

CYP2D6 Inhibitors

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

Digitalis, Clonidine, and Calcium Channel Blockers

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia. If clonidine and a beta blocker, such as metoprolol are co-administered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

ADVERSE EFFECTS

Olmесartan

Reported in clinical trial:

The following adverse reactions occurred in reported clinical trials at an incidence of more than 1% of patients: dizziness, back pain, bronchitis, creatine phosphokinase increased, diarrhea, headache, hematuria, hyperglycemia, hypertriglyceridemia, influenza-like symptoms, pharyngitis, rhinitis and sinusitis. The incidence of cough was similar in placebo (0.7%) and olmesartan (0.9%) patients. Other reported adverse reactions in clinical studies were:

Body as a Whole: chest pain, peripheral edema,

Central and Peripheral Nervous System: vertigo

Gastrointestinal: abdominal pain, dyspepsia, gastroenteritis, nausea

Heart Rate and Rhythm Disorders: tachycardia

Metabolic and Nutritional Disorders: hypercholesterolemia, hyperlipemia, hyperuricemia

Musculoskeletal: arthralgia, arthritis, myalgia *Skin and Appendages:* rash

Facial edema was reported in five patients receiving Olmesartan. Angioedema has been reported with angiotensin II antagonists.

Laboratory Test Findings: In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Olmesartan.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g/dL and 0.3 volume percent, respectively) were observed.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin were observed infrequently.

Five patients (0.1%) assigned to Olmesartan and one patient (0.2%) assigned to placebo in clinical trials were withdrawn because of abnormal liver chemistries (transaminases or total bilirubin). Of the five Olmesartan patients, three had elevated transaminases, which were attributed to alcohol use, and one had a single elevated bilirubin value, which normalized while treatment continued. No additional adverse reaction reported in paediatric population.

Post-Marketing Experience

Body as a Whole: Asthenia, angioedema, anaphylactic reactions

Gastrointestinal: Vomiting

Metabolic and Nutritional Disorders: Hyperkalemia

Musculoskeletal: Rhabdomyolysis

Urogenital System: Acute renal failure, increased blood creatinine levels

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.

Metoprolol:

Reported in clinical trial:

Hypertension and Angina: The most common (> 2%) adverse reactions are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia, and rash.

Heart Failure: Dizziness/vertigo, Bradycardia, Accident and/or injury.

Reported Post-operative Adverse Events: In a randomized, double-blind, placebo-controlled trial of 8351 patients with or at risk for atherosclerotic disease undergoing non-vascular surgery and who were not taking beta-blocker therapy, Metoprolol succinate extended release formulation 100 mg was started 2 to 4 hours prior to surgery then continued for 30 days at 200 mg per day. Metoprolol succinate extended release formulation use was associated with a higher incidence of bradycardia (6.6% vs. 2.4%; HR 2.74; 95% CI 2.19, 3.43), hypotension (15% vs. 9.7%; HR 1.55; 95% CI 1.37, 1.74), stroke (1.0% vs. 0.5%; HR 2.17; 95% CI 1.26, 3.74) and death (3.1% vs. 2.3%; HR 1.33; 95% CI 1.03, 1.74) compared to placebo

Post Marketing Experience:

Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension.

Respiratory: Wheezing (bronchospasm), dyspnea.

Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.

Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.

Hypersensitive Reactions: Pruritus.

Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance

Potential Adverse Reactions: In addition, there are adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Metoprolol succinate extended release formulation.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Laryngospasm, respiratory distress.

Laboratory Test Findings: Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

OVERDOSE

Olmесartan

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 occurs, initiate supportive treatment. The dialyzability of olmesartan is unknown.

Metoprolol

Signs and Symptoms - Overdosage of Metoprolol succinate extended release formulation may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment-Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol, employ the following measures. There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

Bradycardia: Administer intravenous atropine; repeat to effect. If the response is inadequate, consider intravenous isoproterenol or other positive chronotropic agents. Evaluate the need for transvenous pacemaker insertion.

Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.

Bronchospasm: Administer a beta2-agonist, including albuterol inhalation, or an oral theophylline derivative.

Cardiac Failure: Administer diuretics or digoxin for congestive heart failure. For cardiogenic shock, consider IV dobutamine, isoproterenol, or glucagon.

EXPIRY DATE:

Do not use later than the date of expiry

STORAGE:

Store at a temperature not exceeding 30°C, protected from light and moisture.

Keep out of reach of children

PRESENTATION:

Olmator M is available as strip of 10 tablets.

MARKETED BY:



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

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