

For the use only of a Registered Medical Practitioner only

OLMETOR

(Olmesartan medoxomil Tablets)

COMPOSITION

OLMETOR-20

Each film coated tablet contains:
Olmesartan medoxomil I.P. 20 mg
Colour: Titanium Dioxide I.P.

OLMETOR-40

Each film coated tablet contains:
Olmesartan medoxomil I.P. 40 mg
Colour: Titanium Dioxide I.P.

WARNING: FETAL TOXICITY

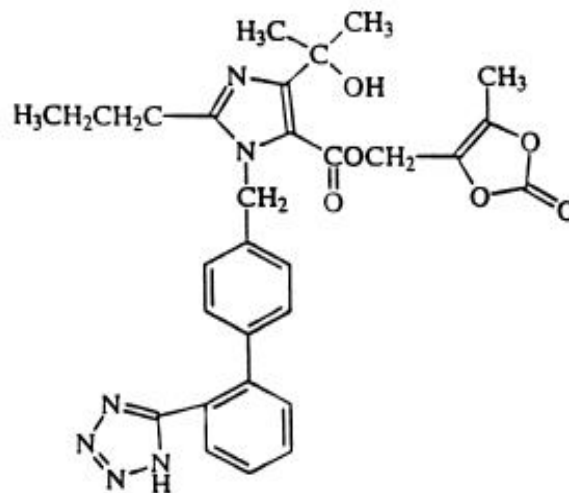
When pregnancy is detected, discontinue product as soon as possible

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

DESCRIPTION

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 2,3-dihydroxy-2-butenyl 4(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is C₂₉H₃₀N₆O₆ and its structural formula is:



CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

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.

PHARMACODYNAMICS

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.

PHARMACOKINETICS

Absorption

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract.

Olmesartan tablets and the suspension formulation prepared from Olmesartan tablets are bioequivalent

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 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 observed in the elderly with repeated dosing; AUC_{ss}, τ was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CL_R.

Pediatric

The pharmacokinetics of olmesartan was studied 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 have not been investigated in pediatric patients less than 1 year of age.

Gender

Minor differences were observed 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-∞} and C_{max} were observed 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 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 C_{max} and 39% reduction in AUC of olmesartan. Lesser effects, 4% and 15% reduction in C_{max} and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride

INDICATIONS

For the treatment of mild to moderate hypertension

DOSAGE AND ADMINISTRATION

Adult Hypertension

Dosage must be individualized. The usual recommended starting dose of Olmesartan is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of Olmesartan may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily.

No initial dosage adjustment is recommended for elderly patients, for patients with moderate to marked renal impairment (creatinine clearance <40 mL/min) or with moderate to marked hepatic dysfunction. 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.

Olmesartan may be administered with or without food.

If blood pressure is not controlled by Olmesartan alone, a diuretic may be added. Olmesartan may be administered with other antihypertensive agents.

Pediatric Hypertension (6 to 16 years of age)

Dosage must be individualized. For children who can swallow tablets, the usual recommended starting dose of Olmesartan is 10 mg once daily for patients who weigh 20 to <35 kg (44 to 77 lb), or 20 mg once daily for patients who weigh ≥35 kg. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of Olmesartan may be increased to a maximum of 20 mg once daily for patients who weigh <35 kg or 40 mg once daily for patients who weigh ≥35 kg.

Children <1 year of age must not receive Olmesartan for hypertension.

CONTRAINDICATIONS

Do not co-administer aliskiren with Olmesartan 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 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-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.

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.

DRUG INTERACTIONS

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 Olmsartan. Monitor serum lithium levels during concomitant use.

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 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 C_{max} 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.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

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.

ADVERSE EVENT

Adult Hypertension

Olmesartan 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 for at least 1 year. Treatment with Olmesartan was well tolerated, with an incidence of adverse reactions similar to placebo. Events generally were mild, transient and had no relationship to the dose of Olmesartan.

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

The following adverse reactions occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with Olmesartan, but also occurred at about the same or greater incidence in patients receiving placebo: 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 potentially important adverse reactions that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in the more than 3100 hypertensive patients treated with Olmesartan monotherapy in controlled or open-label trials are listed below.

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.

Pediatric Hypertension

No relevant differences were identified between the adverse experience profile for pediatric patients aged 1 to 16 years and that previously reported for adult patients.

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, 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

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.

PRESENTATION:

Olmator is 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°C, Protected from moisture

MARKETED BY



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IN/Olmator 20,40mg/Mar 2016/05/PI