



2D Data Matrix to be printed with serial number on each leaflet. The number should not be repeated

Note: Position of the pharma code and product name will change as per the folding machine feasibility

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OLMESARTAN MEDOXOMIL TABLETS safely and effectively. See full prescribing information for OLMESARTAN MEDOXOMIL TABLETS.

OLMESARTAN MEDOXOMIL tablets, for oral use  
Initial U.S. Approval: 2002

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- When pregnancy is detected, discontinue olmesartan medoxomil tablets as soon as possible (5.1, 8.1).
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.1, 8.1).

INDICATIONS AND USAGE

FULL PRESCRIBING INFORMATION

Olmesartan medoxomil tablets are an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension in adult and pediatric patients six years of age and older, alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions (1).

DOSAGE AND ADMINISTRATION

Indication	Starting Dose	Dose Range
Adult Hypertension (2.1)	20 mg once daily	20 - 40 mg once daily
Pediatric Hypertension (6 years of age and older) (2.2)	20 to <35 kg 10 mg once daily ≥35 kg 20 mg once daily	20 to <35 kg 10 - 20 mg once daily ≥35 kg 20 - 40 mg once daily

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 20 mg, and 40 mg (3).

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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adult Hypertension

Olmesartan medoxomil tablets have 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. Events generally were mild, transient and had no relationship to the dose of olmesartan medoxomil tablets.

Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil tablets 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 medoxomil tablets 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 medoxomil tablets and at a higher incidence versus placebo was dizziness (3% vs. 1%).

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

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.

6.2 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 [see Warnings and Precautions (5.5)]

*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, delayed 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.

7 DRUG INTERACTIONS

7.1 Agents Increasing Serum Potassium

Concomitant use of olmesartan with other agents that block the renin-angiotensin system, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium. If co-medication is considered necessary, monitoring of serum potassium is advisable.

7.2 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.

7.3 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 medoxomil tablets and other agents that affect the RAS.

Do not co-administer aliskiren with olmesartan medoxomil tablets in patients with diabetes [see Contraindications (4)]. Avoid use of aliskiren with olmesartan medoxomil tablets in patients with renal impairment (GFR <60 ml/min).

7.4 Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including olmesartan medoxomil tablets. Monitor serum lithium levels during concomitant use.

7.5 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 [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Olmesartan medoxomil can cause fetal harm when administered to a pregnant woman. 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. 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. In animal reproduction studies, olmesartan medoxomil treatment during organogenesis resulted in increased embryofetal toxicity in rats at doses lower than maternally toxic doses.

When pregnancy is detected, discontinue olmesartan medoxomil as soon as possible. Consider alternative antihypertensive therapy during pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.


Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

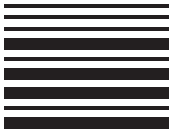
Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death. In patients taking olmesartan medoxomil during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Artwork information			
Customer	Comber	Market	USA
Dimensions (mm)	240 x 450 mm	Non Printing Colors	 Die cut
Pharma Code No.	Front-870 & Back-871		
Printing Colours (01)	Black		
Others:			
Note: Position, Height of the pharma code are tentative, it can be changed based on folding size.			







Closely observe infants with histories of *in utero* exposure to olmesartan medoxomil for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to olmesartan medoxomil, if oliguria or hypotension occurs, utilize measures to maintain adequate blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and supporting renal function.

#### Data

##### Animal Data

No teratogenic effects were observed 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/m<sup>2</sup> basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m<sup>2</sup> 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 observed at doses ≥1.6 mg/kg/day, and delays in developmental milestones (delayed separation of ear auricula, 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 observed at doses ≥ 8 mg/kg/day. The no observed effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

#### 8.2 Lactation

##### Risk Summary

There is no information regarding the presence of olmesartan in human milk, the effects on the breastfed infant, or the effects on milk production. Olmesartan is secreted at low concentration in the milk of lactating rats (*see Data*). 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.

#### Data

Presence of olmesartan in milk was observed after a single oral administration of 5 mg/kg [<sup>14</sup>C] olmesartan medoxomil to lactating rats.

#### 8.4 Pediatric Use

The antihypertensive effects of olmesartan medoxomil were evaluated in one randomized, double-blind clinical study in pediatric patients 1 to 16 years of age [*see Clinical Studies (14.2)*]. The pharmacokinetics of olmesartan medoxomil were evaluated in pediatric patients 1 to 16 years of age [*see Clinical Pharmacology (12.3)*]. Olmesartan medoxomil was generally well tolerated in pediatric patients, and the adverse experience profile was similar to that described for adults.

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

Use of olmesartan medoxomil in children <1 year of age is not recommended [*see Warnings and Precautions (5.2)*]. 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.

#### 8.5 Geriatric Use

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 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 [*see Clinical Pharmacology (12.3)*].

#### 8.6 Hepatic Impairment

Increases in AUC<sub>0 to ∞</sub> and C<sub>max</sub> 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 [*see Clinical Pharmacology (12.3)*].

#### 8.7 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) [*see Dosage and Administration (2.1), Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)*].

#### 8.8 Black Patients

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

#### 10 OVERDOSAGE

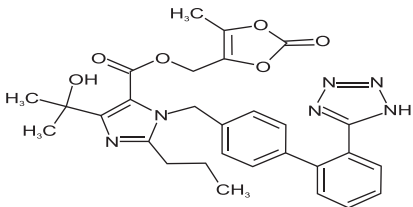
Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension occurs, initiate supportive treatment. The dialyzability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

#### 11 DESCRIPTION

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT<sub>1</sub> subtype angiotensin II receptor antagonist.

Olmesartan medoxomil is described chemically as 1H-imidazole-5-carboxylic acid, 4-(1-hydroxy-1-methyl-ethyl)-2-Propyl-1-[[2'-(1H tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl-, (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester.

Its empirical formula is C<sub>29</sub>H<sub>30</sub>N<sub>6</sub>O<sub>6</sub> and its structural formula is:



Olmesartan medoxomil USP is a white to off-white crystalline powder with a molecular weight of 558.6. It is practically insoluble in water and in heptane, slightly soluble in ethanol (96%), sparingly soluble in methanol. Olmesartan medoxomil is available for oral use as film-coated tablets containing 5 mg, 20 mg, or 40 mg of olmesartan medoxomil and the following inactive ingredients: hydroxypropyl cellulose, hypromellose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide and (5 mg only) yellow iron oxide.

Meet USP Dissolution Test 6.

#### 12 CLINICAL PHARMACOLOGY

##### 12.1 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 AT<sub>1</sub> receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT<sub>2</sub> 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<sub>1</sub> receptor than for the AT<sub>2</sub> 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.

##### 12.2 Pharmacodynamics

Olmesartan medoxomil tablets 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 tablets >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 tablets to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan medoxomil tablets had minimal influence on aldosterone levels and no effect on serum potassium.

##### 12.3 Pharmacokinetics

###### Absorption

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

Olmesartan medoxomil tablets and the suspension formulation prepared from olmesartan medoxomil tablets are bioequivalent [*see Dosage and Administration (2.2)*].

The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (C<sub>max</sub>) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan. Olmesartan medoxomil tablets may be administered with or without food.

###### 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.

###### Specific Populations

###### Geriatric Patients

The pharmacokinetics of olmesartan 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 observed in the elderly with repeated dosing; AUC<sub>0-1</sub> was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CL<sub>R</sub> [*see Dosage and Administration (2.1) and Use in Specific Populations (8.5)*].

###### Pediatric Patients

The pharmacokinetics of olmesartan were 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 [*see Use in Specific Populations (8.4)*]. Olmesartan pharmacokinetics have not been investigated in pediatric patients less than 1 year of age [*see Warnings and Precautions (5.2) and Use in Specific Populations (8.4)*].

###### Male and Female Patients

Minor differences were observed in the pharmacokinetics of olmesartan in women compared to men. AUC and C<sub>max</sub> were 10 to 15% higher in women than in men.

###### Patients with Hepatic Impairment

Increases in AUC<sub>0 to ∞</sub> and C<sub>max</sub> were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60% [*see Dosage and Administration (2.1) and Use in Specific Populations (8.6)*].

###### Patients with Renal Impairment

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 [*see Dosage and Administration (2.1), Warnings and Precautions (5.4) and Use in Specific Populations (8.7)*].

###### Drug Interaction Studies

###### 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<sub>max</sub> and 39% reduction in AUC of olmesartan. Lesser effects, 4% and 15% reduction in C<sub>max</sub> and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride [*see Drug Interactions (7.5)*].

###### Other Studies

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 was not significantly altered by the co-administration of antacids [Al(OH)<sub>3</sub>/Mg(OH)<sub>2</sub>].

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.

#### 13 NONCLINICAL TOXICOLOGY

##### 13.1 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<sup>2</sup> 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.

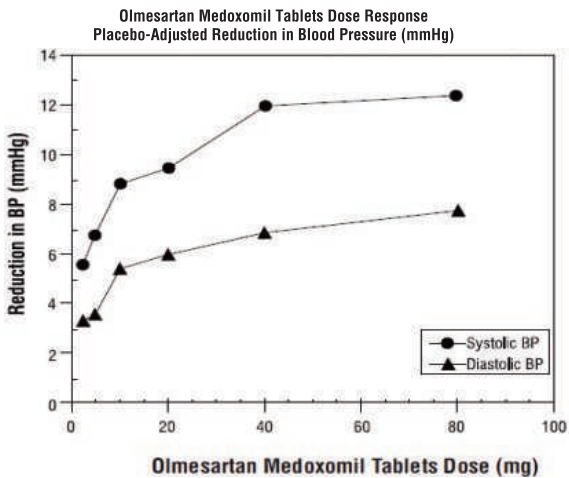
Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese 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.

#### 14 CLINICAL STUDIES

##### 14.1 Adult Hypertension

The antihypertensive effects of olmesartan medoxomil tablets have been demonstrated in seven placebo-controlled studies at doses ranging from 2.5 mg to 80 mg for 6 to 12 weeks, each showing statistically significant reductions in peak and trough blood pressure. A total of 2693 patients (2145 olmesartan medoxomil tablets; 548 placebo) with essential hypertension were studied. Olmesartan medoxomil tablets once daily lowered diastolic and systolic blood pressure. The response was dose related, as shown in the following graph. An olmesartan medoxomil tablets dose of 20 mg daily produces a trough sitting blood pressure (BP) reduction over placebo of about 10/6 mmHg and a dose of 40 mg daily produces a trough sitting BP reduction over placebo of about 12/7 mmHg. Olmesartan medoxomil tablets doses greater than 40 mg had little additional effect. The onset of the antihypertensive effect occurred within 1 week and was largely manifest after 2 weeks.



Data above are from seven placebo-controlled studies (2145 olmesartan medoxomil tablets patients, 548 placebo patients). The blood pressure lowering effect was maintained throughout the 24-hour period with olmesartan medoxomil tablets once daily, with trough-to-peak ratios for systolic and diastolic response between 60 and 80%.

The blood pressure lowering effect of olmesartan medoxomil tablets, with and without hydrochlorothiazide, was maintained in patients treated for up to 1 year. There was no evidence of tachyphylaxis during long-term treatment with olmesartan medoxomil tablets or rebound effect following abrupt withdrawal of olmesartan medoxomil after 1 year of treatment.

The antihypertensive effect of olmesartan medoxomil tablets was similar in men and women and in patients older and younger than 65 years. The effect was smaller in black patients (usually a low-renin population), as has been seen with ACE inhibitors, beta-blockers and other angiotensin receptor blockers. Olmesartan medoxomil tablets had an additional blood pressure lowering effect when added to hydrochlorothiazide.

There are no trials of olmesartan medoxomil tablets demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

##### 14.2 Pediatric Hypertension

The antihypertensive effects of olmesartan medoxomil tablets in the pediatric population were evaluated in a randomized, double-blind study involving 302 hypertensive patients aged 6 to 16 years. The study population consisted of an all-black cohort of 112 patients and a mixed racial cohort of 190 patients, including 38 black patients. The etiology of the hypertension was predominantly essential hypertension (87% of the black cohort and 67% of the mixed cohort). Patients who weighed 20 to <35 kg were randomized to 2.5 or 20 mg of olmesartan medoxomil tablets once daily and patients who weighed ≥35 kg were randomized to 5 or 40 mg of olmesartan medoxomil tablets once daily. At the end of 3 weeks, patients were re-randomized to continuing olmesartan medoxomil tablets or to taking placebo for up to 2 weeks. During the initial dose-response phase, olmesartan medoxomil tablets significantly reduced both systolic and diastolic blood pressure in a weight-adjusted, dose-dependent manner. Overall, the two dose levels of olmesartan medoxomil tablets (low and high) significantly reduced systolic blood pressure by 6.6 and 11.9 mmHg from the baseline, respectively. These reductions in systolic blood pressure included both drug and placebo effect. During the randomized withdrawal to placebo phase, mean systolic blood pressure at trough was 3.2 mmHg lower and mean diastolic blood pressure at trough was 2.8 mmHg lower in patients continuing olmesartan medoxomil tablets than in patients withdrawn to placebo. These differences were statistically different. As observed in adult populations, the blood pressure reductions were smaller in black patients.

In the same study, 59 patients aged 1 to 5 years who weighed ≥5 kg received 0.3 mg/kg of olmesartan medoxomil tablets once daily for three weeks in an open-label phase and then were randomized to receiving olmesartan medoxomil tablets or placebo in a double-blind phase. At the end of the second week of withdrawal, the mean systolic/diastolic blood pressure at trough was 3/3 mmHg lower in the group randomized to olmesartan medoxomil tablets; this difference in blood pressure was not statistically significant (95% C.I. -2 to 7/-1 to 7).

##### 16 HOW SUPPLIED/STORAGE AND HANDLING

Olmesartan medoxomil tablets, USP 5 mg are yellow, round, biconvex film coated tablets debossed with 'H' on one side and 'O1' on the other side and supplied as:

Bottles of 30 tablets	NDC 31722-852-30
Bottles of 90 tablets	NDC 31722-852-90

Olmesartan medoxomil tablets, USP 20 mg are white to off white round, biconvex film coated tablets debossed with 'H' on one side and 'O3' on the other side and supplied as:

Bottles of 30 tablets	NDC 31722-853-30
Bottles of 90 tablets	NDC 31722-853-90

Olmesartan medoxomil tablets, USP 40 mg are white to off white oval, biconvex film coated tablets debossed with 'H' on one side and 'O4' on the other side and supplied as:

Bottles of 30 tablets	NDC 31722-854-30
Bottles of 90 tablets	NDC 31722-854-90

###### Storage

Store at 20° to 25°C (68° to 77°F) [*see USP Controlled Room Temperature*].

##### 17 PATIENT COUNSELING INFORMATION

**Pregnancy:** Advise female patients of childbearing age about the consequences of exposure to olmesartan medoxomil tablets during pregnancy. Discuss treatment options with women planning to become pregnant. Tell patients to report pregnancies to their physicians as soon as possible [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

**Lactation:** Advise nursing women not to breastfeed during treatment with olmesartan medoxomil tablets [*see Use in Specific Populations (8.2)*].

**Hyperkalemia:** Advise patients not to use potassium supplements or salt substitutes that contain potassium without consulting their healthcare provider [*see Drug Interactions (7.1)*].



Manufactured for:  
Camber Pharmaceuticals, Inc.  
Piscataway, NJ 08854.

By: **HETERO™**  
Hetero Labs Limited, Unit V, Polepally, Jadcherla,  
Mahabubnagar - 509 301, India.

Revised: 11/2024

2087434



PRODUCT INFORMATION	
REFERENCE	2024-25\2672-1
STATUS	Finalized, In Process with PKGT
VERSION	1.0
FINALIZED ON	31-12-2024 11:27:11 AM
INITIATED ON	24-12-2024 04:20:32 PM
PRODUCT NAME	OLMESARTAN MEDOXOMIL TABLETS USP
MFG LOCATION	Unit - V Jadcherla
PACK SIZE	na
COUNTRY	USA
MARKET TYPE	Export
MARKETS	CAMBER
COMPONENT	-Printed Product Insert
REQUEST TYPE	New
PRIORITY	High
SPECIFICAITION NUMBER	PMS/2087434-00

SPECIFICATIONS	
DIMENSION	240X450MM
PARMA-CODE	870&871
BAR-CODE	NA
NO OF COLORS	01
BATCH PRE PRINTING	No
VARNISH TYPE	NA

FINALIZATION SUMMARY			
ACTION	DEPARTMENT	ACTION BY	ACTION ON
Initiation & Work allocation	Packaging Development-AW	226066-Prakash Kadtala	24-12-2024 04:22:00 PM
Reviewed	Packaging Development-AW	226066-Prakash Kadtala	24-12-2024 04:24:00 PM
Load Artwork files	Packaging Development-AW	226066-Prakash Kadtala	24-12-2024 04:24:00 PM
Approved	Packaging Development	131144-Suresh Mekala	26-12-2024 04:59:00 PM
Approved	Regulatory Affairs	104116-Prasanna Lakshmi	30-12-2024 01:43:00 PM
Approved	Production	111614-Nohus Reddy	30-12-2024 04:13:00 PM
Finalized	Quality Assurance	121851-Sujan Sarangi	31-12-2024 11:27:00 AM