Olmesartan Medoxomil

Olmezar

20 mg Film-Coated Tablet
40 mg Film-Coated Tablet

ANGIOTENSIN II RECEPTOR BLOCKER / ANTIHYPERTENSIVE

FORMULATION
Each film coated tablet contains:
Olmesartan Medoxomil .....20 mg
Olmesartan Medoxomil .....40 mg

DESCRIPTION
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.
Olmesartan medoxomil, a prodrug, is hydrolyzed to Olmesartan during absorption from the gastrointestinal tract. It is a non-peptide angiotensin II which selectively and competitively inhibits the type 1 Angiotensin II receptors without affecting the other receptors regulating the cardiovascular system.

PHARMACOLOGY
Mechanism of Action
It blocks the vasoconstrictive effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT receptor in vascular smooth muscle.
PHARMACOKINETICS
General
Olmesartan medoxomil is rapidly absorbed and completely bioactivated by ester hydrolysis to Olmesartan during absorption from the gastrointestinal tract. 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 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. 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.
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.
Distribution
The volume of distribution of Olmesartan is approximately 17L. 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. Olmesartan passed across the placental barrier in rats and was distributed to the fetus. Olmesartan was distributed to milk at low levels in rats.

PHARMACODYNAMICS
Olmesartan medoxomil doses of 2.5 to 40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of Olmesartan medoxomil >40 mg giving >90% inhibition at 24 hours. Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increase after single and repeated administration of Olmesartan medoxomil to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg Olmesartan medoxomil had minimal influence on aldosterone levels and no effect on serum potassium.

CLINICAL RESULTS
Approval of Olmesartan is supported by 7 placebo-controlled studies, with doses ranging from 2.5 to 80 mg, given for 6 to 12 weeks. The trials included more than 3275 subjects with essential hypertension. All seven studies reported significant reductions in peak and trough levels of diastolic and systolic blood pressure. Response was dose-related, with 20 mg and 40 mg doses inducing the desired effect and doses over 40 mg having little additional effect. The blood pressure lowering effect from using Olmesartan once-daily was maintained throughout the 24-hour period, with trough-to-peak ratios for systolic and diastolic response between 60 and 80%.

INDICATIONS
For the treatment of hypertension. It may be used alone or in combination with other hypertensive agents.

CONTRAINDICATIONS
Contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS
Fetal/Neonatal Morbidity and Mortality
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. 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 Olmesartan as soon as possible.
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.
Hypotension in Volume- or Salt-Depleted Patients
In patients with activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g. those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with Olmesartan. Treatment should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and. If necessary, given an intravenous infusion of normal saline (See Dosage and Administration). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS
General
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 medoxomil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil.
In studies of ACE inhibitors in patients with unilateral or bilateral artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been a long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Pregnancy: Female patients of chilbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should be told also that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.
DRUG INTERACTIONS
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 a 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.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats 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 Muta Mouse intestine and kidney and for carcinogenicity in mouse bone marrow (micronucleus test) at oral dose 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.
Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS. Fetal/Neonatal Morbidity and Mortality.
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
Safety and effectiveness in pediatric patients have not been established.
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.

ADVERSE REACTIONS
Olmesartan has been evaluated for safety in more than 3825 patients/subjects, including more than 3725 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 events similar to placebo. Events generally were mild, transient and had no relationship to the dose of Olmesartan medoxomil.
The overall frequency of adverse events was not dose-related. Analysis of gender, age, and race groups demonstrated no differences between Olmesartan medoxomil and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e. 79/3278) of patients treated with Olmesartan medoxomil and 2.7% (i.e. 32/1179) of control patients. In placebo-controlled trials, the only adverse event that occurred in more than 1% of patients treated with Olmesartan medoxomil and at a higher incidence versus placebo was dizziness (3% vs. 1%).
The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with Olmesartan medoxomil, 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 events that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in more than 3100 hypertensive patients treated with Olmesartan medoxomil 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
Musculoskeletal: arthralgia, arthritis, myalgia
Skin and Appendages: rash
Facial edema was reported in 5 patients receiving Olmesartan medoxomil. Angioedema has been reported with other angiotensin II antagonists.
Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients (0.1%) assigned to Olmesartan medoxomil 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 medoxomil patients, three had elevated transaminases, which were attributed to alcohol use, and one had a single elevated bilirubin value, which normalized while treatment continued.
Post-Marketing Experience: Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

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 should occur, supportive treatment should be initiated. The dialyzability of Olmesartan is unknown.

DOSAGE AND ADMINISTRATION
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 two 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<40mL/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).
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.

STORE AT TEMPERATURES NOT EXCEEDING 30ºC.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Olmesartan Medoxomil 20 mg Film-Coated Tablet x 50 tablets / box / Alu-alu blister pack of 10's
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