OLMETEC® Film-coated tablets
(Olmesartan medoxomil)

USE IN PREGNANCY

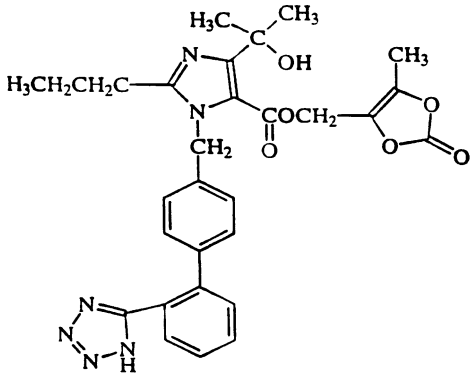
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Olmesartan medoxomil should be discontinued as soon as possible. See Sections **WARNINGS, Fetal/Neonatal Morbidity and Mortality** and **PRECAUTIONS, Pregnancy**.

DESCRIPTION

Olmesartan medoxomil is a prodrug, which is hydrolyzed to the active metabolite olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

Olmesartan medoxomil is described chemically as (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1[[2'-1H-tetrazol-5-yl]-1,1'biphenyl-4-yl]methyl]1H-imidazol-5-carboxylate. Alternatively, it can be described as "2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate".

Its empirical formula is $C_{29}H_{30}N_6O_6$ and its structural formula is:



Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol. Olmetec is available for oral use as film-coated tablets containing 10 mg, 20 mg, or 40 mg of olmesartan medoxomil and the following inactive ingredients: hydroxypropylcellulose, lactose, low substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, talc and titanium dioxide.

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 (RAS), with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT_2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor. Blockade of the RAS 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.

Pharmacokinetics

Absorption and Distribution

Olmesartan medoxomil is rapidly 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 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.

The mean 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.

Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The mean volume of distribution after intravenous dosing is in the range of 16-29 L.

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 30% to 50% of the systematically absorbed drug is excreted in the urine whilst the remainder is excreted in feces (via the bile).

Depending on ethnic origin, the terminal elimination half-life of olmesartan varied between 6 and 15 hours. Steady-state was reached after the first few doses, and no further accumulation was evident with repeated dosing. Renal clearance was approximately 0.5-0.7 L/h.

Pharmacokinetics in Special Populations
Pediatric: The pharmacokinetics of olmesartan have not been investigated in patients <18 years of age.

Elderly: In Caucasian patients, the AUC at steady-state was increased by about 33% in elderly patients. These increases in bioavailability corresponded to reductions in renal clearance of about 30% in elderly.

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.

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.

Hepatic Impairment: Mean olmesartan AUC after single oral administration to patients with moderate hepatic impairment was increased by about 48% compared with healthy controls (total group), or by about 60% when compared with matched controls only.

Drug Interactions
No significant pharmacokinetic interactions were observed 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 antacid (aluminium magnesium hydroxide). 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.

Drug Interaction with Bile Acid Sequestering Agent Colesevelam
Concomitant administration of 40 mg olmesartan medoxomil and 3,750 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 (see Section **PRECAUTIONS**, **Drug Interactions**).

Pharmacodynamics Properties
Angiotensin II is the principal pressor agent of the RAS, with effects that include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium.

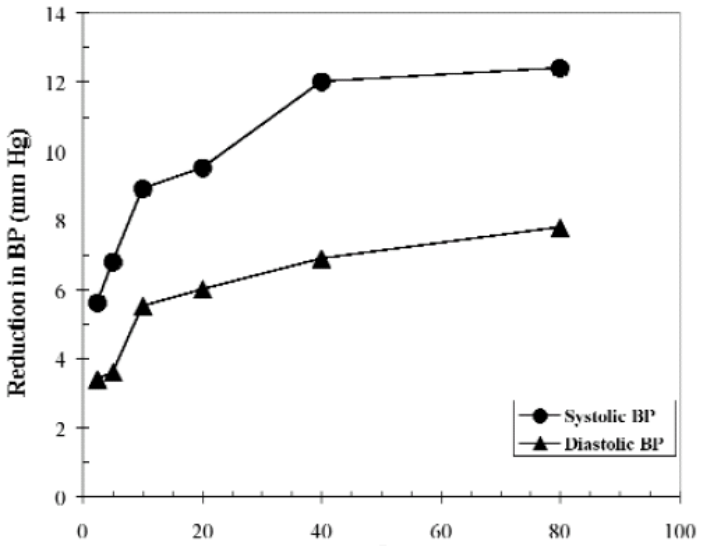
Oral doses of olmesartan medoxomil 2.5 to 40 mg inhibited the pressor response to exogenous angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of olmesartan medoxomil >40 mg giving >90% inhibition at 24 hours.

Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity increased after single or repeated administration of olmesartan medoxomil to healthy subjects or hypertensive patients. Olmesartan medoxomil administration had little effect on plasma levels of aldosterone and no effect on serum potassium.

Clinical Trials

The antihypertensive effects of olmesartan medoxomil have been demonstrated in seven placebo-controlled studies at doses ranging from 2.5 to 80 mg for 6 to 12 weeks, each showing statistically significant reductions in peak and trough blood pressure. A total of 2,693 patients (2,145 olmesartan medoxomil; 548 placebo) with essential hypertension were studied. Olmesartan medoxomil once daily (QD) lowered diastolic and systolic blood pressure. The response was dose-related, as shown in the following graph. An olmesartan medoxomil dose of 20 mg daily produces a trough sitting 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 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.

Olmesartan Medoxomil Dose Response
Placebo-adjusted Reduction
in Blood Pressure (mmHg)



Data above are from seven placebo-controlled studies (2,145 olmesartan medoxomil patients, 548 placebo patients). The blood pressure lowering effect was maintained throughout the 24-hour period with olmesartan medoxomil once daily, with trough-to-peak ratios for systolic and diastolic response between 60% and 80%.

The blood pressure lowering effect of olmesartan medoxomil, 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 or rebound effect following abrupt withdrawal of olmesartan medoxomil after 1 year of treatment.

The antihypertensive effect of olmesartan medoxomil 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 other ACE inhibitors, angiotensin receptor blockers and beta-blockers. Olmesartan medoxomil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The Randomised Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) clinical study included 4,447 patients with type 2 diabetes, normoalbuminuria and at least one additional cardiovascular risk factor. Patients were randomized to olmesartan 40 mg daily or placebo. The trial met its primary endpoint, delayed onset of microalbuminuria. For the secondary endpoints, which the study was not designed to formally assess, cardiovascular events occurred in 96 patients (4.3%) with olmesartan and in 94 patients (4.2%) with placebo. The incidence of cardiovascular mortality was higher with olmesartan compared to placebo treatment (15 patients [0.67%] vs. 3 patients [0.14%] [HR=4.94, 95% CI=1.43-17.06]).

INDICATIONS AND USAGE

Olmesartan medoxomil is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Olmesartan medoxomil is contraindicated in patients who are hypersensitive to any component of the tablet.

Patients who become pregnant should discontinue the use of olmesartan medoxomil as soon as possible. See Section **PRECAUTIONS, Pregnancy** and **Lactation** below.

The concomitant use of olmesartan medoxomil with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m^2) (see Section **PRECAUTIONS**, **Drug Interactions**).

WARNINGS

Pregnancy and Lactation
See Section **PRECAUTIONS, Pregnancy** and **Lactation**.

Fetal/Neonatal Morbidity and Mortality
Drugs that act directly on the RAS 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 ACE inhibitors. When pregnancy is detected, olmesartan medoxomil should be discontinued as soon as possible.

The use of drugs that act directly on the RAS 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 olmesartan medoxomil as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the RAS 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, olmesartan medoxomil should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress 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 towards 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.

There is no clinical experience with the use of olmesartan medoxomil in pregnant women. No teratogenic effects were observed when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1,000 mg/kg/day (240 times the maximum recommended human dose [MRHD] of olmesartan medoxomil on a mg/m^2 basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m^2 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.

Volume- or Salt-depleted Patients with Activated Renin-Angiotensin System
In patients with an activated RAS, 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 medoxomil. 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 Section **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.

Sprue-like Enteropathy
Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan medoxomil months to years after drug initiation. Intestinal biopsies of patients

often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan medoxomil, exclude other etiologies. Consider discontinuation of olmesartan medoxomil in cases where no other etiology is identified.

Electrolyte Imbalance
Olmetec contains olmesartan, a drug that inhibits the RAS. Drugs that inhibit the RAS can cause hyperkalemia. Monitor serum electrolytes periodically.

Dual Blockade of the Renin-Angiotensin System (RAS)
There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Section **PRECAUTIONS**, **Drug Interactions**).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

PRECAUTIONS

General
Impaired Renal Function: As a consequence of inhibiting the RAS, changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil. In patients whose renal function may depend predominantly on the activity of the RAS (e.g., patients with severe congestive heart failure), treatment with 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 medoxomil (see Section **CLINICAL PHARMACOLOGY**, **Pharmacokinetics in Special Populations**).

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

There is an increased risk of renal insufficiency when patients with bilateral renal artery stenosis (or stenosis of the artery to a single functioning kidney) are treated with medicinal products that affect the RAS.

Information for Patients
Pregnancy: Female patients of childbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the RAS 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

Use with Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including olmesartan. Therefore, use of olmesartan medoxomil and lithium in combination is not recommended. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Dual Blockade of the Renin-Angiotensin System

Clinical trial data has shown that dual blockade of the RAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events, such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAS-acting agent (see Sections **CONTRAINDICATIONS** and **WARNINGS**).

Use with Aliskiren

Do not co-administer aliskiren with olmesartan medoxomil in patients with diabetes (see Section **CONTRAINDICATIONS**) because dual use is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Avoid use of aliskiren with olmesartan medoxomil in patients with renal impairment (GFR <60 mL/min).

Non-steroidal Anti-inflammatory Agents (NSAIDs) 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 and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including olmesartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Use with Colesevelam Hydrochloride

Concurrent administration of bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect (see Section **CLINICAL PHARMACOLOGY, Drug Interactions**).

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 (2,000 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 1,000 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 Muta Mouse 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 1,000 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
Use of drugs that act directly on the RAS during the second and third trimesters of pregnancy has been associated with fetal injury and even death. Patients who become pregnant whilst using olmesartan medoxomil should discontinue treatment as soon as possible.

If Olmetec is used during pregnancy, or if the patient becomes pregnant while taking Olmetec, the patient should be apprised of the potential hazard to a fetus. Should exposure to Olmetec have occurred from the second trimester forward, ultrasound examinations of the renal function and of the skull are recommended. Newborns exposed to angiotensin II antagonists *in utero* must be closely monitored for the occurrence of hypotension, oliguria, and hyperkalaemia. See Section **WARNINGS, Fetal/Neonatal Morbidity and Mortality**.

Lactation
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 medoxomil in clinical studies, more than 20% were 65 years of age and above, 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.

UNDESIRABLE EFFECTS

Olmesartan medoxomil has been evaluated for safety in more than 3,825 patients/subjects, including more than 3,275 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 medoxomil 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 racial 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. 79/3,278) of patients treated with olmesartan medoxomil and 2.7% (i.e. 32/1,179) 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 medoxomil (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 the more than 3,100 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, hyperlipemia, hyperuricemia.

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.

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

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 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.

Clinical Trial Experience
Dizziness has been reported commonly (≥1%, <10% incidence) in clinical trials with olmesartan medoxomil.

Post-launch Experience
In post-launch experience, adverse drug reactions which have been reported very rarely (<0.01% incidence) are: Peripheral edema, headache, cough, abdominal pain, nausea, vomiting, diarrhea, sprue-like enteropathy, anaphylactic reaction, rash, pruritus, angioedema, acute renal failure, hepatic enzymes increased, blood creatinine increased, hyperkalemia, myalgia and asthenic conditions, such as asthenia, fatigue, lethargy, malaise. 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.

No information is available regarding the dialyzability of olmesartan.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. The usual recommended starting dose of olmesartan medoxomil 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 medoxomil 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 (see Section **CLINICAL PHARMACOLOGY**, **Pharmacokinetics in Special Populations**). For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), olmesartan medoxomil should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see Section **WARNINGS**, **Volume- or Salt-depleted Patients with Activated Renin-Angiotensin System**).

Olmesartan medoxomil may be administered with or without food.

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

PRECLINICAL SAFETY DATA

Preclinical carcinogenicity studies revealed no clinically relevant risk for humans. In reproductive studies in rats, olmesartan medoxomil did not affect fertility. In common with other angiotensin II receptor antagonists, survival of offspring was reduced following exposure to olmesartan medoxomil, and pelvic dilatation of the kidney was seen after exposure of the dams in late pregnancy and lactation. In common with other antihypertensive agents, olmesartan medoxomil was shown to be more toxic to pregnant rabbits than to pregnant rats; however, there was no indication of a fetotoxic effect.

PHARMACEUTICAL FORM

Olmesartan medoxomil is available for oral use as tablets containing 5 mg, 10 mg, 20 mg or 40 mg olmesartan medoxomil, although not all strengths are supplied in every country.

PHARMACEUTICAL INFORMATION

The inactive ingredients in olmesartan medoxomil tablets comprise: microcrystalline cellulose, low substituted hydroxypropylcellulose, lactose, hydroxypropylcellulose and magnesium stearate.

In those countries where the tablets are film-coated, the film coat contains the following ingredients: talc, titanium dioxide, hypromellose and yellow iron oxide (5 mg tablet only).

SHELF LIFE

3 years

NATURE AND CONTENTS OF CONTAINER

Laminated polyamide/aluminum/polyvinyl chloride/aluminum blister pack.

Packs of 10, 14, 28, 30, 56, 98 and 100 film-coated tablets.

Not all pack sizes may be marketed.

STORAGE

No special precaution for storage. Store at below 25°C.

PRODUCT OWNER

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