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

OLMETOR-H
(Olmesartan Medoxomil and Hydrochlorothiazide Tablets)

COMPOSITION

OLMETOR-H 20

Each film coated tablet contains:
Olmesartan Medoxomil I.P. 20 mg
Hydrochlorothiazide I.P. 12.5 mg
Colors: Yellow Oxide of Iron, Red Oxide of Iron and Titanium Dioxide I.P.

OLMETOR-H 40

Each film coated tablet contains:
Olmesartan Medoxomil I.P.40 mg
Hydrochlorothiazide I.P. 12.5 mg
Excipients q.s.
Colors: Red Oxide of Iron,Yellow Oxide of Iron and Titanium Dioxide I.P.

WARNING: FETAL TOXICITY

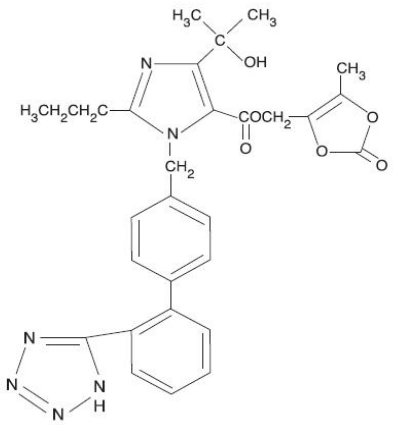
When pregnancy is detected, discontinue Olmesartan as soon as possible.

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

DESCRIPTION

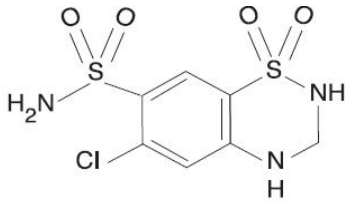
Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

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]imidazole5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is $C_{29}H_{30}N_6O_6$ and its structural formula is:



Hydrochlorothiazide
Hydrochlorothiazide is a white, or practically white, crystalline powder. Hydrochlorothiazide is slightly soluble in water but freely soluble in sodium hydroxide solution.

Chemical Name: Hydrochlorothiazide is 6-chloro-3, 4-dihydro-2*H*-1, 2, 4-benzo-thiadiazine- 7-sulfonamide 1, 1-dioxide. Molecular Weight: 297.7 Molecular Formula: $C_7H_8ClN_3O_4S_2$



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS:

Olmetor-H is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Once daily dosing with Olmetor-H provides an effective and smooth reduction in blood pressure over the 24 hour dose interval. The effects of fixed dose combination of olmesartan medoxomil/hydrochlorothiazide on mortality and cardiovascular morbidity are currently unknown.

Mechanism of Action

Olmesartan medoxomil
The effect of olmesartan medoxomil on mortality and morbidity is not yet known. 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_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 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 rennin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure. In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting

reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy. With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the anti hypertensive effect of thiazides is not fully understood. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 hours. Epidemiological studies have shown that long-term treatment with hydrochlorothiazide monotherapy reduces the risk of cardiovascular mortality and morbidity.

PHARMACOKINETICS

General

Olmesartan medoxomil
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 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.

Hydrochlorothiazide
When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism and Excretion

Olmesartan medoxomil
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.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Distribution
Olmesartan
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.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

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

Geriatrics:
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; $AUC_{ss,\tau}$ was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CL_R. Systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly patients compared to young healthy volunteers.

Gender:
Minor differences were observed in the pharmacokinetics of olmesartan in women compared to men. AUC and Cmax were 10-15% higher in women than in men.

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. The half-life of hydrochlorothiazide is prolonged in patients with impaired renal function.

Hepatic Insufficiency:
Increases in AUC and C_{max} for olmesartan were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%.Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide.

INDICATIONS

Olmetor-H is indicated for the treatment of mild to moderate hypertension in adults (Not indicated for initial therapy.)

DOSAGE AND ADMINISTRATION

Dose Titration by Clinical Effect

Olmetor-H is available in strengths of 20 mg/12.5 mg. A patient whose blood pressure is inadequately controlled by Olmesartan or hydrochlorothiazide alone may be switched to once daily Olmetor-H (olmesartan medoxomil-hydrochlorothiazide). Dosing should be individualized. Depending on the blood pressure response, the dose may be titrated at intervals of 2-4 weeks. If blood pressure is not controlled by Olmesartan alone, hydrochlorothiazide may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily. If a patient is taking hydrochlorothiazide, Olmesartan may be added starting with a dose of 20 mg once daily and titrated to 40 mg, for inadequate blood pressure control.

If large doses of hydrochlorothiazide have been used as monotherapy and volume depletion or hyponatremia is present, caution should be used when adding Olmesartan or switching to Olmesartan Hydrochlorothiazide as marked decreases in blood pressure may occur. The dose of Olmetor-H is one tablet once daily. More than one tablet daily is not recommended. Olmetor-H may be administered with other antihypertensive agents.

Replacement Therapy

Olmetor-H (Olmesartan Medoxomil-Hydrochlorothiazide) may be substituted for its titrated components.

Elderly

In elderly patients the same dosage of the combination is recommended as for adults.

Patients with Renal Impairment

The usual regimens of therapy with Olmetor-H may be followed provided the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Olmetor-H is not recommended.

Patients with Hepatic Impairment

Olmetor-H should be used with caution in patients with mild to moderate hepatic impairment. In patients with moderate hepatic impairment, an initial dose of 10 mg olmesartan medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are receiving diuretics and/or other antihypertensive agents. There is no experience of olmesartan medoxomil in patients with severe hepatic impairment. Olmetor-H should not be used in patients with severe hepatic impairment, cholestasis and biliary obstruction.

CONTRAINDICATIONS

Hypersensitivity to the active substances, to any of the excipients or to other sulfonamidederived substances (since hydrochlorothiazide is a sulfonamide-derived medicinal product).

- Severe renal impairment (creatinine clearance < 30 mL/min).
- Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia.
- Severe hepatic impairment, cholestasis and biliary obstructive disorders.Second and third trimester of pregnancy

WARNINGS

Olmesartan

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 and Hydrochlorothiazide 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 and hydrochlorothiazide, 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 and hydrochlorothiazide for hypotension, oliguria, and hyperkalemia.

There is no clinical experience with the use of olmesartan and hydrochlorothiazide in pregnant women. No teratogenic effects were observed when 1.6:1 combinations of olmesartan medoxomil and hydrochlorothiazide were administered to pregnant mice at oral doses up to 1625 mg/kg/day (122 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or pregnant rats at oral doses up to 1625 mg/kg/day (280 times the MRHD on a mg/m^2 basis). In rats, however, fetal body weights at 1625 mg/kg/day (a toxic, sometimes lethal dose in the dams) were significantly lower than control. The no observed effect dose for developmental toxicity in rats, 162.5 mg/kg/day, is about 28 times, on a mg/m^2 basis, the MRHD of olmesartan and hydrochlorothiazide (40 mg olmesartan medoxomil /25 mg hydrochlorothiazide/day).

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume- or Salt-Depleted Patients
In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (*e.g.*, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with olmesartan and hydrochlorothiazide, as with any angiotensin receptor blocker. 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. When electrolyte and fluid imbalances have been corrected, therapy usually can be continued without difficulty. A transient hypotensive response is not a contraindication to further treatment.

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.

Hydrochlorothiazide
Hepatic Impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction
Lithium generally should not be given with thiazides.

Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

PRECAUTIONS

General

Olmesartan medoxomil-hydrochlorothiazide

In a double-blind clinical trial of various doses of olmesartan medoxomil and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.4 mEq/L) was 2.1%; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%. In this trial, no patient discontinued due to increases or decreases in serum potassium.

Hydrochlorothiazide

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis and hypokalemia. Serum and urine electrolyte determinations are important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia.

Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

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 reninangiotensin-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 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.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Information for Patients
Pregnancy:
Female patients of childbearing age should be told about the consequences of exposure to olmesartan and hydrochlorothiazide during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension:
A patient receiving olmesartan and hydrochlorothiazide should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, olmesartan and hydrochlorothiazide should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea or vomiting can lead to an excessive fall in blood pressure, with the same consequences of light-headedness and possible syncope.

DRUG INTERACTIONS

Olmesartan

No significant drug interactions were reported in studies in which Olmesartan was coadministered with digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [$Al(OH)_3/Mg(OH)_2$]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including olmesartan medoxomil, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving olmesartan medoxomil and NSAID therapy.

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

Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on Olmesartan and other agents that affect the RAS.

Do not co-administer aliskiren with Olmesartan in patients with diabetes. Avoid use of aliskiren with Olmesartan in patients with renal impairment (GFR <60 ml/min).

Colesevelam hydrochloride

Concurrent administration of bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Consider administering olmesartan at least 4 hours before the colesevelam hydrochloride dose.

Lithium

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

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, Or Narcotics – potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin) – dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs – additive effect or potentiation.

Cholestyramine and Colestipol Resins – absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH – intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g. Norepinephrine) – possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g. Tubocurarine) possible increased responsiveness to the muscle relaxant.

Lithium – should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparation with olmesartan medoxomil-hydrochlorothiazide.

Non-steroidal Anti-inflammatory Drugs – in some patients the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when olmesartan medoxomil-hydrochlorothiazide tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

USE IN SPECIFIC POPULATIONS

Olmesartan

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 Cmax 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
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 p^{53} 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.

Hydrochlorothiazide
Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male

and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, or in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations. It was also not genotoxic *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, or the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, the Mouse Lymphoma Cell (mutagenicity) assay and the *Aspergillus nidulans* non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

ADVERSE REACTIONS

Olmesartan medoxomil-hydrochlorothiazide

Olmesartan medoxomil-hydrochlorothiazide has been evaluated for safety in 1243 hypertensive patients. Treatment with olmesartan medoxomil-hydrochlorothiazide 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-hydrochlorothiazide.

In the clinical trials, the overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil-hydrochlorothiazide and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.0% (25/1243) of patients treated with olmesartan medoxomil-hydrochlorothiazide and 2.0% (7/342) of patients treated with placebo.

In a placebo-controlled clinical trial, the following adverse events reported with olmesartan medoxomil-hydrochlorothiazide occurred in >2% of patients, and more often on the olmesartan medoxomil-hydrochlorothiazide combination than on placebo, regardless of drug relationship:

	Olmesartan/HCTZ (N=247) (%)	**Placebo (N=42) (%)**	**Olmesartan (N=125) (%)**	**HCTZ (N=88) (%)**
Gastrointestinal				
Nausea	3	0	2	1
Metabolic				
Hyperuricemia	4	2	0	2
Nervous System				
Dizziness	9	2	1	8
Respiratory				
Upper Respiratory Tract Infection	7	0	6	7

The following adverse events were also reported at a rate of >2%, but were as, or more, common in the placebo group: headache and urinary tract infection.

Other adverse events that have been reported with an incidence of greater than 1.0%, whether or not attributed to treatment, in the more than 1200 hypertensive patients treated with olmesartan medoxomil-hydrochlorothiazide in controlled or open-label trials are listed below.

Body as a Whole: chest pain, back pain, peripheral edema

Central and Peripheral Nervous System: vertigo

Gastrointestinal: abdominal pain, dyspepsia, gastroenteritis, diarrhea

Liver and Biliary System: SGOT increased, GGT increased, SGPT increased

Metabolic and Nutritional: hyperlipemia, creatine phosphokinase increased, hyperglycemia

Musculoskeletal: arthritis, arthralgia, myalgia

Respiratory System: coughing

Skin and Appendages Disorders: rash

Urinary System: hematuria

Facial edema was reported in 2/1243 patients receiving olmesartan medoxomilhydrochlorothiazide. Angioedema has been reported with angiotensin II receptor antagonists.

Olmesartan medoxomil
Other 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 tachycardia and hypercholesterolemia.

Hydrochlorothiazide
Other adverse experiences that have been reported with hydrochlorothiazide, with out regard to causality, are listed below:

Body as a Whole: weakness

Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

Metabolic: hyperglycemia, glycosuria, hyperuricemia

Musculoskeletal: muscle spasm

Nervous System/Psychiatric: restlessness

Renal: renal failure, renal dysfunction, interstitial nephritis

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

Special Senses: transient blurred vision, xanthopsia

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

Creatinine, Blood Urea Nitrogen: Increases in blood urea nitrogen (BUN) and serum creatinine of >50% were observed in 1.3% of patients. No patients were discontinued from clinical trials of olmesartan medoxomil-hydrochlorothiazide due to increased BUN or creatinine.

Hemoglobin and Hematocrit: A greater than 20% decrease in hemoglobin and hematocrit was observed in 0.0 % and 0.4% (one patient), respectively, of olmesartan medoxomil-hydrochlorothiazide patients, compared with 0.0% and 0.0%, respectively

Post-Marketing Experience
The following adverse reactions have been reported in post-marketing experience:
Body as a Whole: Asthenia, angioedema, anaphylactic reactions, peripheral edema

Gastrointestinal: Vomiting, diarrhea, sprue-like enteropathy (see WARNINGS, *Sprue-like Enteropathy*)

Metabolic and Nutritional Disorders: Hyperkalemia

Musculoskeletal: Rhabdomyolysis

Urogenital System: Acute renal failure, increased blood creatinine levels

Skin and Appendages: Alopecia, pruritus, urticarial

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

Olmesartan medoxomil

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.

No lethality was observed in acute toxicity studies in mice and rats given single oral doses up to 2000 mg/kg olmesartan medoxomil. The minimum lethal oral dose of olmesartan medoxomil in dogs was greater than 1500 mg/kg.

Hydrochlorothiazide

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has

not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

PRESENTATION:
Olmetor-H is available in strips of 10's tablets.

EXPIRY DATE:
Do not use later than the date of expiry.

STORAGE AND HANDLING INSTRUCTIONS:
Store at a temperature not exceeding 30°C, protected from light and moisture.
Keep out of reach of children.

MARKETED BY

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