

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-532

APPROVED LABELING

BENICAR HCT™ Tablets

(OLMESARTAN MEDOXOMIL-HYDROCHLOROTHIAZIDE)

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, BENICAR HCT™ should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

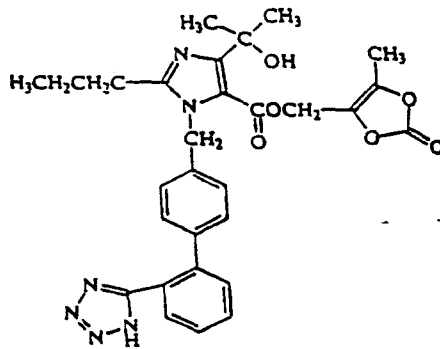
DESCRIPTION

BENICAR HCT™ (olmesartan medoxomil-hydrochlorothiazide) is a combination of an angiotensin II receptor antagonist (AT₁ subtype), olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide (HCTZ).

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract.

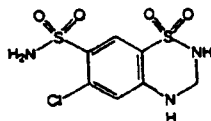
Olmesartan medoxomil is 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate.

Its empirical formula is C₂₉H₃₀N₆O₆ and its structural formula is:



Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.6. It is practically insoluble in water and sparingly soluble in methanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.7. Hydrochlorothiazide is slightly soluble in water but freely soluble in sodium hydroxide solution.

BENICAR HCT™ is available for oral administration in tablets containing 20 mg or 40 mg of olmesartan medoxomil combined with 12.5 mg of hydrochlorothiazide, or 40 mg of olmesartan medoxomil combined with 25 mg of hydrochlorothiazide. Inactive ingredients include: hydroxypropylcellulose, hypromellose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, red iron oxide, talc, titanium dioxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Olmesartan medoxomil

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT₂ receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT₁ receptor than for the AT₂ receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan medoxomil does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and

circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

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 antihypertensive effect of thiazides is not fully understood.

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 have not been investigated in patients <18 years of age.

Geriatric: 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; $AUC_{ss, \tau}$ was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CL_R .

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 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.

Hepatic Insufficiency: Increases in $AUC_{0-\infty}$ 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%.

Drug Interactions: See PRECAUTIONS, Drug Interactions.

Pharmacodynamics

Olmesartan medoxomil

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.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Clinical Trials

Olmesartan medoxomil

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 2693 patients (2145 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. An olmesartan medoxomil dose of 20 mg daily produces a trough sitting BP reduction over placebo of about 10/6 mm Hg and a dose of 40 mg daily produces a trough sitting BP reduction over placebo of about 12/7 mm Hg. 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.

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.

Olmesartan medoxomil-hydrochlorothiazide

In clinical trials 1230 patients were exposed to the combination of olmesartan medoxomil (2.5 mg to 40 mg) and hydrochlorothiazide (12.5 mg to 25 mg). These trials included one placebo-controlled factorial trial (n=502) in mild-moderate hypertensives with combinations of olmesartan medoxomil (10 mg, 20 mg, 40 mg or placebo) and hydrochlorothiazide (12.5 mg, 25 mg or placebo). The antihypertensive effect of the combination on trough blood pressure was related to the dose of each component (see table below).

Placebo-Adjusted Changes in Sitting Systolic/Diastolic Blood Pressure (mmHg)

HCTZ dose	Olmesartan Medoxomil dose			
	0 mg	10 mg	20 mg	40 mg
0 mg	--	7/5	12/5	13/7
12.5 mg	5/1	17/8	17/8	16/10
25 mg	14/5	19/11	22/11	24/14

Once-daily dosing with 20 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide, 40 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide or 40 mg olmesartan medoxomil and 25 mg hydrochlorothiazide produced mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) ranging from 17/8 to 24/14 mm Hg.

The onset of the antihypertensive effect occurred within 1 week and was near maximal at 4 weeks. The antihypertensive effect was independent of gender, but there were too few subjects to identify response differences based on race or age greater than or less than 65 years. No appreciable changes in trough heart rate were observed with combination therapy in the placebo-controlled trial.

INDICATIONS AND USAGE

BENICAR HCT™ is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**)

CONTRAINDICATIONS

BENICAR HCT™ is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system 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 angiotensin converting enzyme inhibitors. When pregnancy is detected, BENICAR HCT™ should be discontinued as soon as possible.

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; 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 BENICAR HCT™ as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system 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, BENICAR HCT™ should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress 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 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.

There is no clinical experience with the use of BENICAR HCT™ 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/m² basis) or pregnant rats at oral doses up to 1625 mg/kg/day (280 times the MRHD on a mg/m² 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/m² basis, the MRHD of BENICAR HCT™ (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 BENICAR HCT™, 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 (See **DOSAGE AND ADMINISTRATION**). 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.

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 (see **PRECAUTIONS: Drug Interactions; Hydrochlorothiazide, Lithium**)

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 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. (See **CLINICAL PHARMACOLOGY, 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.

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 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.

Symptomatic Hypotension: A patient receiving BENICAR HCT™ 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, BENICAR HCT™ 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 medoxomil

No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with hydrochlorothiazide, 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.

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, Non depolarizing (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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Olmesartan medoxomil-hydrochlorothiazide

No carcinogenicity studies with olmesartan medoxomil-hydrochlorothiazide have been conducted.

Olmesartan medoxomil-hydrochlorothiazide in a ratio of 20:12.5 was negative in the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation test up to the maximum recommended plate concentration for the standard assays. Olmesartan medoxomil and hydrochlorothiazide were tested individually and in combination ratios of 40:12.5, 20:12.5 and 10:12.5, for clastogenic activity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. A positive response was seen for each component and combination ratio. However, no synergism in clastogenic activity was detected between olmesartan medoxomil and hydrochlorothiazide at any combination ratio. Olmesartan medoxomil-hydrochlorothiazide in a ratio of 20:12.5, administered orally, tested negative in the *in vivo* mouse bone marrow erythrocyte micronucleus assay at administered doses of up to 3144 mg/kg.

No studies of impairment of fertility with olmesartan medoxomil-hydrochlorothiazide have been conducted.

Olmesartan medoxomil

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/m² 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 both 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.

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.

Thiazides appear in human milk. 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

Clinical studies of BENICAR HCT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

Olmesartan and hydrochlorothiazide are substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

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 medoxomil-hydrochlorothiazide. Angioedema has not been reported with olmesartan medoxomil or olmesartan medoxomil-hydrochlorothiazide, but has been reported with other 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, without 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, in placebo-treated patients. No patients were discontinued due to anemia.

Post-Marketing Experience: Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

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.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of BENICAR® (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 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 (see **CLINICAL PHARMACOLOGY, Special Populations**). For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), BENICAR® should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see **WARNINGS, Hypotension in Volume- or Salt-Depleted Patients**).

Hydrochlorothiazide is effective in doses between 12.5 mg and 50 mg once daily.

The side effects (see **WARNINGS**) of BENICAR® are generally rare and independent of dose; those of hydrochlorothiazide are most typically dose-dependent (primarily hypokalemia). Some dose-independent phenomena (e.g., pancreatitis) do occur with hydrochlorothiazide. Therapy with any combination of olmesartan medoxomil and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

Replacement Therapy

BENICAR HCT™ (olmesartan medoxomil-hydrochlorothiazide) may be substituted for its titrated components.

Dose Titration by Clinical Effect

BENICAR HCT™ is available in strengths of 20 mg/12.5 mg, 40 mg/12.5 mg and 40 mg/25 mg. A patient whose blood pressure is inadequately controlled by BENICAR® or hydrochlorothiazide alone may be switched to once daily BENICAR HCT™ (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 BENICAR® 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, BENICAR®™ 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 BENICAR® or switching to BENICAR HCT™ as marked decreases in blood pressure may occur (see **WARNINGS, Hypotension in Volume- or Salt-Depleted Patients**). Consideration should be given to reducing the dose of hydrochlorothiazide to 12.5 mg before adding BENICAR®.

The antihypertensive effect of BENICAR HCT™ is related to the dose of both components over the range of 10 mg/12.5 mg to 40 mg/25 mg (see CLINICAL PHARMACOLOGY, Clinical Trials). The dose of BENICAR HCT™ is one tablet once daily. More than one tablet daily is not recommended.

BENICAR HCT™ may be administered with other antihypertensive agents.

Patients with Renal Impairment

The usual regimens of therapy with BENICAR HCT™ 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 BENICAR HCT™ is not recommended.

Patients with Hepatic Impairment

No dosage adjustment is necessary with hepatic impairment (see CLINICAL PHARMACOLOGY, Special Populations).

HOW SUPPLIED

BENICAR HCT™ is supplied as 20 mg/12.5 mg: reddish-yellow, circular, film-coated tablets, approximately 8.5 mm in diameter, with "Sankyo" debossed on one side and "C22" on the other side. Each tablet contains 20 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide.

40 mg/12.5 mg: reddish-yellow, oval, film-coated tablets, approximately 15 x 7 mm, with "Sankyo" debossed on one side and "C23" on the other side. Each tablet contains 40 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide.

40 mg/25 mg: pink, oval, film-coated tablets, approximately 15 x 7 mm, with "Sankyo" debossed on one side and "C25" on the other side. Each tablet contains 40 mg of olmesartan medoxomil and 25 mg of hydrochlorothiazide.

Tablets are supplied as follows:

	20 mg/12.5 mg	40 mg/12.5 mg	40 mg/25 mg
Bottle of 30 tablets	NDC 65597-105-30	NDC 65597-106-30	NDC 65597-107-30
Bottle of 90 tablets	NDC 65597-105-90	NDC 65597-106-90	NDC 65597-107-90
10 Blister cards of 10 tablets	NDC 65597-105-10	NDC 65597-106-10	NDC 65597-107-10
Bottle of 1000 tablets	NDC 65597-105-11	NDC 65597-106-11	NDC 65597-107-11

Storage

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature].

- Manufactured for Sankyo Pharma Inc., Parsippany, NJ 07504

Manufactured by Sankyo Pharma GmbH, Munich, Germany

Rx Only

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/s/

Doug Throckmorton
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