

PRODUCT MONOGRAPH

Pr **OLMETEC PLUS**[®]

Olmesartan Medoxomil and Hydrochlorothiazide

20 mg/12.5 mg, 40 mg/12.5 mg,
and 40 mg/25 mg Tablets

Angiotensin II AT₁ Receptor Blocker – Diuretic

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Pr^oOLMETEC PLUS[®]

Olmesartan Medoxomil and Hydrochlorothiazide

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet/ 20 mg/12.5 mg, 40 mg/12.5 mg, and 40 mg/25 mg	hydroxypropylcellulose, hypromellose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, red iron oxide, talc, titanium dioxide and yellow iron oxide

INDICATIONS AND CLINICAL USE

OLMETEC PLUS is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

OLMETEC PLUS is not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**).

Geriatrics (≥65 years of age): Reported clinical experience has not identified differences in responses between elderly and younger patients, however, greater sensitivity of some older individuals cannot be ruled out (see **DOSAGE AND ADMINISTRATION**).

Pediatrics (<18 years of age): The safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Because of the hydrochlorothiazide component, OLMETEC PLUS (olmesartan medoxomil and hydrochlorothiazide) is contraindicated in patients with anuria, and in patients who are hypersensitive to other sulfonamide-derived drugs.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT₁) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, OLMETEC PLUS (olmesartan medoxomil and hydrochlorothiazide) should be discontinued as soon as possible (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Cardiovascular

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 OLMETEC PLUS. Treatment should start under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. 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.

Valvular Stenosis: there is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion, because they do not develop as much afterload reduction.

Endocrine and Metabolism

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 during thiazide therapy 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.

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

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

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

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 hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides may decrease PBI levels without signs of thyroid disturbance.

Hyperglycemia may occur with thiazide diuretics. Insulin or oral hypoglycemic agents requirements in diabetic patients may be altered and latent diabetes mellitus may become manifest during thiazide diuretic therapy.

Hepatic/Biliary/Pancreatic

No adjustment of dosage is required for patients with mild hepatic impairment. Data is lacking with respect to the use of 20 mg and 40 mg olmesartan medoxomil; therefore a lower starting dose is recommended in patients with moderate liver disease, and the maximum dose of 20 mg/12.5 mg olmesartan medoxomil-hydrochlorothiazide daily should not be exceeded. Care should be exercised in patients with liver disease, especially in those patients with biliary obstructive disorders, as the majority of olmesartan is eliminated in the bile. No information is available in patients with severe liver disease; therefore, use of OLMETEC in this group of patients is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

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.

Renal

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, acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil (see **ACTION AND 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.

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

Sensitivity/Resistance

Hypersensitivity: Anaphylactic reactions have been reported very rarely in patients treated with olmesartan.

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.

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

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.

Special Populations

Pregnant Women: drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, OLMETEC PLUS should be discontinued as soon as possible.

The use of ARBs is not recommended during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARB, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

Infants with a history of in utero exposure to ARBs 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 a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

It is not known if olmesartan can be removed from the body by hemodialysis.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

Animal Data

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 OLMETEC PLUS (40 mg olmesartan medoxomil/25 mg hydrochlorothiazide/day).

Nursing Women: It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Thiazides appear in human milk. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (<18 years of age): The safety and effectiveness in pediatric patients have not been established.

Geriatrics (≥65 years of age): Reported clinical experience has not identified differences in responses between elderly and younger patients, however, greater sensitivity of some older individuals cannot be ruled out (see **CLINICAL TRIALS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Olmesartan medoxomil-hydrochlorothiazide

Olmesartan medoxomil-hydrochlorothiazide has been evaluated for safety in 1243 patients treated for essential hypertension. 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 discontinuations 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. The following potentially serious adverse reactions have been reported with OLMETEC/OLMETEC PLUS in controlled trials: syncope, hypotension.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a placebo-controlled clinical trial, the following adverse events were reported with olmesartan medoxomil-hydrochlorothiazide in >1% of patients (Table 1).

Table 1: Adverse Events^a Occurring >1% in Placebo-controlled Cohort

	Total Placebo ALONE	Total HCTZ ALONE	Total Olmesartan Medoxomil ALONE	Total Olmesartan Medoxomil + HCTZ
	(N = 42)	(N = 88)	(N = 125)	(N = 247)
System Organ Class (SOC)				
MedDRA Preferred Term	N (%)	N (%)	N (%)	N (%)
Ear and labyrinth disorders				
Ear disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.0%)
Gastrointestinal disorders				
Nausea	0 (0.0%)	1 (1.1%)	2 (1.6%)	7 (2.8%)
Abdominal pain	1 (2.4%)	1 (1.1%)	4 (3.2%)	5 (2.0%)
Dyspepsia	0 (0.0%)	4 (4.5%)	2 (1.6%)	5 (2.0%)
Diarrhea	1 (2.4%)	2 (2.3%)	4 (3.2%)	4 (1.6%)
Gastroenteritis	1 (2.4%)	0 (0.0%)	0 (0.0%)	3 (1.2%)
General disorders and administration site conditions				
Fatigue	0 (0.0%)	1 (1.1%)	3 (2.4%)	5 (2.0%)
Influenza like illness	0 (0.0%)	1 (1.1%)	1 (0.8%)	3 (1.2%)
Immune system disorders				
Hypersensitivity	0 (0.0%)	1 (1.1%)	1 (0.8%)	3 (1.2%)
Infections and Infestations				
Upper respiratory tract infection	0 (0.0%)	6 (6.8%)	8 (6.4%)	16 (6.5%)
Urinary tract infections	1 (2.4%)	1 (1.1%)	1 (0.8%)	8 (3.2%)
Pharyngitis	0 (0.0%)	1 (1.1%)	1 (0.8%)	4 (1.6%)
Rhinitis	2 (4.8%)	0 (0.0%)	3 (2.4%)	4 (1.6%)
Sinusitis	1 (2.4%)	2 (2.3%)	3 (2.4%)	3 (1.2%)
Injury, poisoning and procedural complications				
Injury	0 (0.0%)	3 (3.4%)	1 (0.8%)	6 (2.4%)
Metabolism and nutrition disorders				
Hyperuricemia	1 (2.4%)	2 (2.3%)	0 (0.0%)	10 (4.0%)
Hyperglycemia	1 (2.4%)	2 (2.3%)	0 (0.0%)	5 (2.0%)
Hyperlipemia	0 (0.0%)	1 (1.1%)	1 (0.8%)	4 (1.6%)
BUN increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.6%)
Musculoskeletal and connective tissue disorders				
Back pain	1 (2.4%)	2 (2.3%)	3 (2.4%)	5 (2.0%)
Myalgia	0 (0.0%)	1 (1.1%)	4 (3.2%)	5 (2.0%)
Nervous system disorders				
Dizziness	1 (2.4%)	7 (8.0%)	1 (0.8%)	23 (9.3%)
Headache	3 (7.1%)	4 (4.5%)	11 (8.8%)	13 (5.3%)

Table 1: Adverse Events^a Occurring >1% in Placebo-controlled Cohort

	Total Placebo ALONE	Total HCTZ ALONE	Total Olmesartan Medoxomil ALONE	Total Olmesartan Medoxomil + HCTZ
	(N = 42)	(N = 88)	(N = 125)	(N = 247)
System Organ Class (SOC)				
MedDRA Preferred Term	N (%)	N (%)	N (%)	N (%)
Renal and urinary disorders				
Hematuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (2.4%)
Pyuria	0 (0.0%)	1 (1.1%)	1 (0.8%)	4 (1.6%)
Urine analysis abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.6%)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0.0%)	0 (0.0%)	2 (1.6%)	5 (2.0%)
Vascular disorders				
Hypotension	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.2%)

^a Adverse events reported in >1% of patients in the Total Olmesartan Medoxomil + HCTZ treatment group.

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.

Gastrointestinal disorders: abdominal pain, dyspepsia, diarrhea.

General disorders and administration site conditions: chest pain, edema peripheral.

Infections and infestations: gastroenteritis.

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, creatine phosphokinase increased, gamma-glutamyltransferase increased.

Musculoskeletal and connective tissue disorders: arthritis, arthralgia, back pain, myalgia.

Nervous system disorders: vertigo.

Renal and urinary disorders: hematuria.

Respiratory, thoracic and mediastinal disorders: cough.

Skin and subcutaneous tissue disorders: rash.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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

Abnormal Hematologic and Clinical Chemistry Findings

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

Liver Functions Tests: elevations of liver enzymes and/or serum bilirubin were observed infrequently.

	<u>Placebo</u> (n=42)	<u>HCTZ</u> (n=88)	<u>Olmesartan Medoxomil</u> (n=125)	<u>Olmesartan Medoxomil + HCTZ</u> (n=247)
CPK increased	2 (4.8%)	2 (2.3%)	3 (2.4%)	4 (1.6%)
γGT increased	1 (2.4%)	1 (1.1%)	3 (2.4%)	3 (1.2%)
ALT increased	2 (4.8%)	1 (1.1%)	3 (2.4%)	3 (1.2%)
AST increased	1 (2.4%)	1 (1.1%)	3 (2.4%)	3 (1.2%)

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-Market Adverse Drug Reactions

Other adverse events reported rarely in post-marketing use include: asthenia, angioedema, vomiting, hyperkalemia, rhabdomyolysis, renal failure acute, blood creatinine increased, alopecia, pruritus, urticaria, palpitations, syncope, and blood uric acid increased.

Anaphylactic reactions have been reported very rarely in patients treated with olmesartan.

DRUG INTERACTIONS

Drug-Drug Interactions

Olmesartan medoxomil-hydrochlorothiazide

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, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Renal function should be monitored 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

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

OLMETEC PLUS and NSAID agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

Olmesartan medoxomil

Diuretics

Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction in blood pressure after initiation of therapy with olmesartan. The possibility of symptomatic hypotension with the use of olmesartan can be minimized by discontinuing the diuretic prior to initiation of treatment (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension in Volume- or Salt-Depleted Patients**). No drug interaction of clinical significance has been identified with thiazide diuretics.

Warfarin

There was no effect on either the pharmacokinetics or pharmacodynamics of warfarin when co-administered with olmesartan medoxomil in healthy volunteers.

Digoxin

No pharmacokinetics or pharmacodynamics effects were reported when olmesartan medoxomil was co-administered with digoxin in healthy volunteers.

Antacids

The bioavailability of olmesartan was not significantly altered when co-administered with antacids [Al(OH)₃/Mg(OH)₂].

Cytochrome P450 Enzyme System

Unlike some other angiotensin II receptor blockers, olmesartan medoxomil is not metabolized by cytochrome P450 enzymes. Interactions with drugs that inhibit, induce or are metabolized by these enzymes are not expected.

Hydrochlorothiazide

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

Agents Increasing Serum Potassium

Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increase in serum potassium.

Since olmesartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium when olmesartan medoxomil therapy is initiated. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that olmesartan may have on serum potassium.

Alcohol, Barbiturates, or Narcotics

Potential of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin)

Due to the potential for hyperglycemia in patients on thiazides, dosage adjustment of the antidiabetic drug may be required.

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 may occur.

Lithium Salts

As with other drugs which eliminate sodium, lithium clearance may be reduced in the presence of olmesartan. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered with olmesartan medoxomil. Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Other Antihypertensive Drugs

Diuretic additive effect or potentiation of anti-hypertensive effect may occur.

Pressor Amines (e.g., Norepinephrine)

In the presence of diuretics, possible decreased response to pressor amines may occur but the effect is not sufficient to preclude their use.

Skeletal Muscle Relaxants, Non depolarizing (e.g., Tubocurarine)

Thiazide drugs may increase responsiveness to the muscle relaxant.

Drug-Food Interactions

OLMETEC PLUS may be administered with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- OLMETEC PLUS (olmesartan medoxomil and hydrochlorothiazide) is not for initial therapy.
- The dosage must be individualized.

- 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.
- The dose of OLMETEC PLUS should be determined by the titration of the individual components.

Recommended Dose and Dosage Adjustment

Replacement Therapy

Once the patient has been stabilized on the individual components as described below, OLMETEC PLUS may be substituted if the doses on which the patient was stabilized are the same as those in the fixed combination.

Dose Titration by Clinical Effect

OLMETEC PLUS 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 olmesartan medoxomil or hydrochlorothiazide alone may be switched to once daily OLMETEC PLUS. Dosage should be individualized. Depending on the blood pressure response, the dose may be titrated at intervals of 2-4 weeks.

The antihypertensive effect of OLMETEC PLUS is related to the dose of both components over the range of 10 mg/12.5 mg to 40 mg/25 mg (see **ACTION AND CLINICAL PHARMACOLOGY**). The dose of OLMETEC PLUS is one tablet once daily. More than one tablet daily is not recommended.

Elderly: No adjustment of dose is generally required in elderly patients (see below for dose recommendation in patients with renal impairment). If up-titration to the maximum dose of 40 mg/25 mg daily is required, blood pressure should be closely monitored (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

Hepatic Impairment: No adjustment of dosage is required for patients with mild hepatic impairment. Data is lacking with respect to the use of 20 mg and 40 mg olmesartan medoxomil; therefore, a lower starting dose is recommended in patients with moderate liver disease, and the maximum dose of 20 mg/12.5 mg olmesartan medoxomil-hydrochlorothiazide daily should not be exceeded. Care should be exercised in patients with liver disease, especially in those patients with biliary obstructive disorders, as the majority of olmesartan is eliminated in the bile. No information is available in patients with severe liver disease; therefore, use of OLMETEC in this group of patients is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Renal Impairment: Owing to the limited experience of higher dosages in this patient group, the maximum dose in patients with mild to moderate renal impairment is 20 mg/12.5 mg once daily. The use of olmesartan medoxomil in patients with severe renal impairment is not recommended, since there is only limited experience in this patient group. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so OLMETEC PLUS is not recommended.

For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), OLMETEC PLUS should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see **WARNINGS AND PRECAUTIONS, Renal**).

The side effects (see **WARNINGS AND PRECAUTIONS**) of olmesartan medoxomil 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.

Olmesartan Medoxomil Monotherapy

The usual recommended starting dose of olmesartan medoxomil monotherapy is 20 mg once daily 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.

- **Elderly:** No adjustment of dose is generally required in elderly patients (see below for dose recommendation in patients with renal impairment). If up-titration to the maximum dose of 40 mg daily is required, blood pressure should be closely monitored (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).
- **Hepatic Impairment:** No adjustment of dosage is required for patients with mild hepatic impairment. Data is lacking with respect to the use of 20 mg and 40 mg olmesartan medoxomil; therefore, a lower starting dose is recommended in patients with moderate liver disease, and the maximum dose of 20 mg/12.5 mg olmesartan medoxomil-hydrochlorothiazide daily should not be exceeded. Care should be exercised in patients with liver disease, especially in those patients with biliary obstructive disorders, as the majority of olmesartan is eliminated in the bile. No information is available in patients with severe liver disease; therefore, use of OLMETEC in this group of patients is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).
- **Renal Impairment:** Owing to the limited experience of higher dosages in this patient group, the maximum dose in patients with mild to moderate renal impairment is 20 mg olmesartan medoxomil once daily. The use of olmesartan medoxomil in patients with severe renal impairment is not recommended, since there is only limited experience in this patient group.

For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), OLMETEC PLUS should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see **WARNINGS AND PRECAUTIONS, Renal**).

If blood pressure is not controlled by olmesartan medoxomil alone, hydrochlorothiazide may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily.

Hydrochlorothiazide is effective in doses between 12.5 mg and 50 mg once daily. If a patient is taking hydrochlorothiazide, olmesartan medoxomil 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 medoxomil or switching to OLMETEC PLUS as marked decreases in blood pressure may occur (see **WARNINGS AND PRECAUTIONS, Renal**). Consideration should be given to reducing the dose of hydrochlorothiazide to 12.5 mg before adding olmesartan medoxomil.

Missed Dose

If patients miss a dose, they should wait until their next scheduled dose. Patients should not double their dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Olmesartan medoxomil

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

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 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.

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.

Pharmacokinetics

Absorption:

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.

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.

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.

Special Populations and Conditions

Pediatrics (<18 years of age): The pharmacokinetics of olmesartan have not been investigated in patients <18 years of age.

Geriatrics (≥65 years of age): 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 but statistically significant 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 . However, the clinical relevance is unknown.

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.

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

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%.

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.

STORAGE AND STABILITY

Store at 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DOSAGE FORM: OLMETEC PLUS (olmesartan medoxomil and hydrochlorothiazide) is available as film-coated tablets.

COMPOSITION: OLMETEC PLUS is supplied as:

20 mg/12.5 mg: reddish-yellow, circular, film-coated tablets, approximately 8.5 mm in diameter, with "C22" debossed on one 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 "C23" debossed on one 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 "C25" debossed on one side. Each tablet contains 40 mg of olmesartan medoxomil and 25 mg of hydrochlorothiazide.

All tablet strengths contain the following inactive ingredients: hydroxypropylcellulose, hypromellose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, red iron oxide, talc, titanium dioxide and yellow iron oxide.

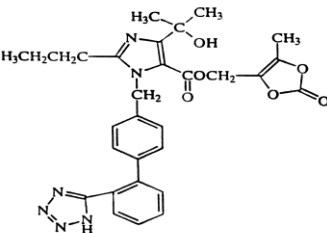
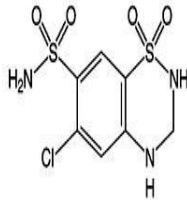
PACKAGING:

20 mg/12.5 mg, 40 mg/12.5 mg, and 40 mg/25 mg tablets: Blister cards of 7 tablets (4 cards/carton).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper/common name:	Olmesartan medoxomil	Hydrochlorothiazide
Chemical name:	1 <i>H</i> -imidazole-5-carboxylic acid, 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl]-4yl]methyl]-,(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester	6-chloro-3,4-dihydro-2 <i>H</i> -1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide
Molecular formula and molecular mass:	C ₂₉ H ₃₀ N ₆ O ₆ 558.6	C ₇ H ₈ ClN ₃ O ₄ S ₂ 297.7
Structural formula:		

Physicochemical properties:

- white to pale yellowish-white powder
- practically insoluble in water and sparingly soluble in methanol.
- white, or practically white, crystalline powder
- slightly soluble in water but freely soluble in sodium hydroxide solution.

The dissociation constant (pKa) of olmesartan medoxomil was determined by the UV method to be 4.3, when measured at 20°C in Britton Robinson buffer solution (I = 0.5).

The pKa values are 8.6 and 9.9 (Dollery's Therapeutic Drugs quotes 7.9 and 9.2)

CLINICAL TRIALS

Study demographics and trial design

The antihypertensive effects of olmesartan medoxomil-hydrochlorothiazide have been demonstrated in clinical trials in which 1230 of 2757 patients with mild to moderate essential hypertension were exposed to a combination of olmesartan medoxomil (2.5 mg to 40 mg) and hydrochlorothiazide (12.5 mg to 25 mg). These clinical 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) for 8 weeks. Across treatment groups, the percentage of male patients ranged from 48.7% to 65.9% and the mean age ranged from 49.9 to 54.7 years. At least 58.1% in all treatment groups were Caucasian and most patients (at least 76.1%) were <65 years of age.

Study results

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 systolic and diastolic blood pressure reductions at trough (24 hours post-dosing) ranging from 17/8 to 24/14 mm Hg, respectively. The antihypertensive effect of the combination on trough blood pressure was related to the dose of each component (see table below). No appreciable changes in trough heart rate were observed with combination therapy in the placebo-controlled trial.

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*

The onset of the antihypertensive effect occurred within 1 week and was near maximal at 4 weeks of treatment. All 6 dose combinations were statistically significantly more effective than placebo in lowering sitting diastolic blood pressure at Week 8 ($P < 0.05$). The placebo-adjusted decrease in sitting diastolic blood pressure was approximately additive as follows: 5 mm Hg to 9 mm Hg for 10 mg to 40 mg olmesartan medoxomil + 12.5 mg HCTZ and 9 mm Hg to 14 mm Hg for 10 mg to 40 mg olmesartan medoxomil + 25 mg HCTZ, compared to 3 mm Hg to 6 mm Hg for 10 mg to 40 mg olmesartan medoxomil alone and 2 mm Hg to 5 mm Hg for 12.5 mg to 25 mg HCTZ alone.

Results of secondary efficacy variable analysis sitting systolic blood pressure demonstrated that the 6 olmesartan medoxomil + HCTZ combinations produced effects similar to those observed for sitting diastolic blood pressure at Week 8. The reduction in systolic blood pressure generally was more pronounced than the reduction in diastolic blood pressure. The placebo-adjusted decrease in sitting systolic blood pressure was approximately additive as follows: 14 mm Hg to 17 mm Hg for 10 mg to 40 mg olmesartan medoxomil + 12.5 mg HCTZ and 20 mm Hg to 24 mm Hg for 10 mg to 40 mg olmesartan medoxomil + 25 mg HCTZ, compared to 7 mm Hg to

13 mm Hg for 10 mg to 40 mg olmesartan medoxomil alone and 6 mm Hg to 14 mm Hg for 12.5 mg to 25 mg HCTZ alone. Results of the analyses of standing diastolic and systolic blood pressures were consistent with those of sitting blood pressure.

The results of the responder rate analysis were consistent with the results of the analyses of the change in blood pressure from baseline to Week 8. The responder rate increased when HCTZ was combined with olmesartan medoxomil, and also increased with increasing olmesartan medoxomil and HCTZ dose. The highest responder rate (92%) was observed for the highest dose of the combination (40 mg olmesartan medoxomil + 25 mg HCTZ).

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. The blood pressure lowering effect of olmesartan medoxomil-hydrochlorothiazide combination was maintained in long-term studies for up to 2 years. The overall response to the combination treatment was similar in Black and non-Black patients in the placebo-controlled trial.

Administered doses of 10 mg, 20 mg, or 40 mg olmesartan medoxomil combined with 12.5 mg or 25 mg hydrochlorothiazide was shown to be well tolerated and statistically significantly more effective than placebo in lowering sitting diastolic blood pressure at Week 8. The magnitude of blood pressure reduction increased with increasing dose of olmesartan medoxomil and HCTZ. There was no evidence of a rebound effect in sitting diastolic blood pressure after discontinuation of olmesartan medoxomil + HCTZ.

In a supportive Phase III placebo-controlled, double-blind multi-centre study of 20 mg olmesartan medoxomil combined with either HCTZ 12.5 mg or 25 mg in patients with essential hypertension not controlled by olmesartan monotherapy, statistical significant evidence of reduction in mean daytime diastolic BP was achieved after eight weeks of combined therapy with the 25 mg HCTZ dose, but not with the 12.5 mg HCTZ dose. However, efficacy of the 12.5 mg HCTZ dose was demonstrated in eight other supportive trials.

Clinical studies of OLMETEC PLUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see **CLINICAL TRIALS**).

DETAILED PHARMACOLOGY

Animal Pharmacology

The results of clinical and nonclinical pharmacology studies demonstrated that olmesartan, the active form of olmesartan medoxomil, is an AII receptor antagonist that binds selectively and competitively to the AT₁ receptor, with negligible binding to the AT₂ receptor. Olmesartan was shown to be both a potent and long-lasting AII antagonist in both humans and animals.

The antihypertensive effect of olmesartan depends on the activity of the renin-angiotensin system, as demonstrated by its effectiveness in different animal models of hypertension. In rat

models, olmesartan is most effective in renal hypertensive rats, followed by spontaneously hypertensive rats, normotensive rats, and DOCA-salt hypertensive rats. Olmesartan also significantly decreased blood pressure in Goldblatt hypertensive Beagle dogs. The antihypertensive effect is dose-dependent and has a long duration of action. From hemodynamic studies conducted with olmesartan medoxomil, it appears that the antihypertensive effect is due to dilation of blood vessels throughout the body; however, regional blood flow in major organs is unaffected except for the kidney, where blood flow is markedly increased. It was also demonstrated that olmesartan ameliorated hypertension- and diabetic induced nephropathy in different rat models.

General pharmacology studies demonstrated that olmesartan had little effect on a variety of physiological systems, except for those that would be expected based on its pharmacology activity. Therefore, it is expected that olmesartan would produce minimal adverse effects at pharmacological doses.

Co-administration of olmesartan medoxomil and HCTZ (at ratios of 1:10 and 1:100) decreased blood pressure in spontaneously hypertensive rats to a greater extent than olmesartan medoxomil or HCTZ administered alone, indicating that there was an additive effect on blood pressure. Plasma renin activity was increased in animals treated with olmesartan medoxomil or olmesartan medoxomil/HCTZ, due to the pharmacological activity of olmesartan. Urine volume and total excretion of sodium and potassium was increased in animals treated with HCTZ or olmesartan medoxomil/HCTZ, due to the pharmacological activity of HCTZ.

TOXICOLOGY

Acute Toxicity

Olmesartan medoxomil has low oral acute toxicity in mice, rats and dogs. Doses up to 2000 mg/kg were administered to rats and mice and 1500 mg/kg to dogs with no clinical signs or mortality. Intravenous toxicity studies were conducted with olmesartan, the active metabolite, in mice and rats. Severe clinical signs occurred at all doses administered in mice (≥ 1700 mg/kg) and rats (≥ 1400 mg/kg) with lethality in mice at ≥ 1850 mg/kg and at ≥ 1550 mg/kg in rats.

Long Term Toxicity

Oral repeat dose toxicity studies were conducted in mice, rats and dogs with olmesartan medoxomil. Repeat dose (14-day) intravenous studies were conducted with olmesartan (the active metabolite) in rats and dogs. These studies demonstrated that olmesartan medoxomil was well tolerated at doses up to 4000 mg/kg/day in mice (90 days), 1000 mg/kg/day in rats (6 months) and 160 mg/kg/day in dogs (12 months). There were no treatment-related clinical findings at these dose levels. Severe clinicopathological effects associated with uremia necessitated the early necropsy of one dog administered 500 mg/kg (90-day study).

Hematological effects (decreased RBC count, hemoglobin, hematocrit, prothrombin time, activated partial thromboplastin time) in rodents, clinical chemistry changes (increase in BUN and creatinine) in rodents and dogs, and histopathological findings in kidneys of rodents and

dogs were observed. In kidney, hypertrophy and hyperplasia of the juxtaglomerular apparatus, accompanied by an increase in cytoplasmic granularity are considered to be due to the pharmacological effects of olmesartan on the Renin-Angiotensin System. At high doses, renal tubular regeneration was observed in rats and dogs and progressive increase in chronic neuropathy was observed in rats.

Decreased heart weights, observed in mice and rats were attributed to a decrease in heart muscle load following a reduction in blood pressure.

Saline as a water source in rats treated with olmesartan medoxomil attenuated/eliminated the observed effect.

The findings from studies in rats and dogs where olmesartan was administered IV for 14 days were consistent with the above-mentioned findings observed after oral administration.

Similarly, olmesartan medoxomil + HCTZ in combination showed effects on the kidneys which were considered to be secondary to the pharmacological activity of olmesartan and HCTZ. Oral administration of olmesartan medoxomil/HCTZ to rats for 26 weeks resulted in histopathological changes in the kidneys which were part of the spectrum of changes associated with chronic progressive nephropathy in rats. The NOAEL was 16.25 mg/kg/day in rats. The results of the 26-week oral toxicity study in dogs demonstrated that olmesartan medoxomil/HCTZ produced hypertrophy and eosinophilia of the renal tubules. The NOAEL for olmesartan medoxomil/HCTZ was 6.5 mg/kg/day for males, based on the tubular eosinophilia observed at ≥ 13 mg/kg/day, and 52 mg/kg/day for females.

Mutagenicity

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, for clastogenicity in mouse bone marrow (micronucleus test), DNA repair in the UDS assay and DNA fragmentation in the Comet assay at oral doses of up to 2000 mg/kg.

Olmesartan medoxomil-HCTZ was negative in the *in vitro* bacterial reverse mutation test up to concentrations of 5411 $\mu\text{g}/\text{plate}$ and *in vivo* mouse bone marrow micronucleus test in a ratio of 20:12.5 mg/kg, at doses up to 3144 mg/kg. There was no synergism in clastogenic activity between olmesartan medoxomil and HCTZ in combination ratios of 40:12.5, 20:12.5 and 10:12.5 $\mu\text{g}/\text{mL}$, in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay.

Carcinogenicity

Oncogenicity studies demonstrated that olmesartan medoxomil was not carcinogenic when administered at doses up to 2000 mg/kg/day to rats for up to 2 years (equivalent to about 480 times the maximum recommended human dose (MRHD) of 40 mg/day on a mg/m^2 basis).

A 26-week oncogenicity study conducted in the transgenic mouse strain C57BL/6 TacfBR-[KO] N5 p53(+/-) treated with up to 1000 mg/kg/day (about 120 times the MRHD) olmesartan medoxomil revealed no evidence of carcinogenic potential. No carcinogenicity studies were conducted with olmesartan medoxomil and hydrochlorothiazide.

Reproduction Studies

There was no effect on fertility in rats at doses up to 1000 mg/kg/day (240 times the MRHD) of olmesartan medoxomil. No teratogenic effects and no significant effects on the number of corpora lutea, implants and dead/live fetuses were observed in rats at doses up to 1000 mg/kg/day and in rabbits at doses up to 1 mg/kg/day. Perinatal/postnatal toxicity studies in rats demonstrated that a NOAEL for developmental toxicity is 0.3 mg/kg/day of olmesartan medoxomil.

Olmesartan/HCTZ had no effect on embryo-fetal development in mice. Embryo-fetal toxicity studies conducted in rats treated with olmesartan medoxomil/HCTZ at doses up to 1625 mg/kg/day produced developmental delays related to the extent of maternal toxicity; the developmental NOAEL for this effect was 162.5 mg/kg/day. No perinatal/postnatal studies were conducted with olmesartan medoxomil/HCTZ.

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PART III: CONSUMER INFORMATION**PrOLMETEC PLUS®**

(Olmesartan medoxomil and hydrochlorothiazide)

This leaflet is part III of a three-part "Product Monograph" published when OLMETEC PLUS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OLMETEC PLUS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

OLMETEC PLUS is used to lower blood pressure where treatment with just one drug is not effective.

High blood pressure increases the workload of the heart and arteries. If this condition continues for a long time, damage to the blood vessels of the brain, heart, and kidneys can occur, and may eventually result in a stroke, heart or kidney failure. High blood pressure also increases the risk of heart attacks. Reducing your blood pressure decreases your risk of developing these illnesses.

What it does:

OLMETEC PLUS contains a combination of two drugs. The drug olmesartan medoxomil acts to inhibit the naturally occurring hormone, angiotensin II in the human body that causes the blood vessels to constrict. The drug hydrochlorothiazide acts by inducing diuresis (urination) which leads to decreased amount of body water which is beneficial in patients with high blood pressure.

When it should not be used:

Do not take OLMETEC PLUS if you:

- are allergic to olmesartan medoxomil, hydrochlorothiazide, or to any other ingredient;
- are allergic to sulphonamide-derived drugs;
- are pregnant or plan to become pregnant. If this is the case, talk to your doctor as soon as possible;
- are breastfeeding.

OLMETEC PLUS is not recommended for use in children and adolescents (below the age of 18 years).

If you are not sure whether you should start taking OLMETEC PLUS, contact your physician or pharmacist.

What the medicinal ingredients are:

Olmesartan medoxomil and hydrochlorothiazide

What the important nonmedicinal ingredients are:

Hydroxypropylcellulose, hypromellose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, red iron oxide, talc, titanium dioxide and yellow iron oxide.

What dosage forms it comes in:

Film-Coated Tablets: 20 mg/12.5 mg (reddish-yellow, circular shaped), 40 mg/12.5 mg (reddish-yellow, oval shaped), or 40 mg/25 mg (pink, oval shaped).

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

OLMETEC PLUS should not be used during pregnancy. If you discover that you are pregnant while taking OLMETEC PLUS, stop the medication and please contact your physician.

BEFORE you use OLMETEC PLUS talk to your doctor or pharmacist if:

- You perform tasks which may require special attention (for example driving a vehicle or operating dangerous machinery). You should not perform these tasks until you know how you respond to your medication.
- You are taking other medicines to control your blood pressure.
- You are taking any medication including non-prescription or herbal products.
- You have recently suffered from excess vomiting or diarrhea.
- You have liver or kidney disease, gout, diabetes, lupus erythematosus, or if you are being treated with other diuretics (water tablets).
- You have difficulty urinating.
- You are allergic to penicillin or sulfonamide-derived drugs.
- You have to undergo any kind of surgery and general anesthesia.
- You are pregnant or breastfeeding.
- You are allergic to this drug or its ingredients or components of the container.

Allergic reactions can occur in patients treated with OLMETEC PLUS.

One of the medicines in OLMETEC PLUS can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting OLMETEC PLUS. Tell your doctor right away if you have:

- decrease in vision
- eye pain

If OLMETEC PLUS is taken with medicines to reduce pain and swelling (called Non-steroidal anti-inflammatory drugs (NSAIDs) or with COX-2 inhibitors), you may experience:

- decreased kidney function or sudden kidney failure. If you notice a decrease in the amount of urine you produce, generalized swelling, weakness, shortness of breath, or irregular heartbeats, loss of appetite, lethargy, and fatigue, contact your doctor or go to the emergency department of the hospital right away.
- A decreased ability of OLMETEC PLUS to lower your blood pressure. This means that OLMETEC PLUS may not be able to lower your blood pressure as it is expected to do. If this happens, speak with your doctor or pharmacist.

Taking OLMETEC PLUS during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you are planning to become pregnant while taking OLMETEC PLUS, contact immediately your doctor.

It is possible that OLMETEC PLUS passes into breast milk. You should discuss with your doctor about taking OLMETEC PLUS while breastfeeding.

INTERACTIONS WITH THIS MEDICATION

As with most medications, interaction with other drugs is possible. Therefore, do not take any other medication, including non-prescription and prescription drugs, unless you have discussed it with your doctor or your pharmacist. Drugs that may interact with OLMETEC PLUS include:

- Medicines used to lower blood pressure, including diuretics (water pills)
- Potassium-sparing diuretics (water pills)
- Potassium supplements or salt substitutes containing potassium
- Lithium salts
- Antidiabetic agents (insulin)
- Resins which reduce high cholesterol level
- Corticosteroids
- Medicines used to reduce pain and swelling called Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 Inhibitors
- Sympathomimetics
- Anesthetics
- Certain pain and arthritis medicines
- Curare derivatives (muscle relaxants)
- Allopurinol (anti-gout treatment)
- Amantadine
- Cytotoxic drugs (cancer therapy)
- Anticholinergic agents
- Cyclosporine
- Digoxin (a heart medicine)

Avoid alcoholic beverages until you have discussed their use with your physician. Alcohol consumption may alter your blood pressure.

PROPER USE OF THIS MEDICATION

Dosage must be individualized. OLMETEC PLUS is not for initial therapy.

Usual dose:

The usual recommended dose is in the range of 20/12.5 to 40/25 mg once a day. Take OLMETEC PLUS every day exactly as your physician has instructed in order to maintain your blood pressure.

OLMETEC PLUS may be taken with or without food.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Try to take OLMETEC PLUS daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unintended or undesirable effects, so-called side effects. Although most patients do not experience side effects when taking OLMETEC PLUS, some patients may experience dizziness, headache, nausea, fatigue, and upper respiratory tract infection.

Tell your doctor or pharmacist about these or any other unusual symptoms.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Uncommon	Allergic Reactions (rash, swelling of the lips, face or neck, difficulty breathing or speaking)			√
	Hypotension (dizziness or light-headedness including fainting may occur due to low blood pressure)			√
	Bronchitis (shortness of breath, weakness, high fever, coughing and fatigue)		√	
	Eye problems that may lead to vision loss (decrease in vision, eye pain)		√	
Rare	Sudden Kidney Failure (sudden decrease or absence of urine, generalized swelling, weakness, shortness of breath, or irregular heartbeats, loss of appetite, lethargy and fatigue)			√

This is not a complete list of side effects. For any unexpected effects while taking OLMETEC PLUS, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 15-30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

or at Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at 1-800-567-2594
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-496-9092, or
 - Mail to: Merck Canada Inc.
Pharmacovigilance
P.O. Box 1005
Pointe-Claire-Dorval, QC
H9R 4P8

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program or Merck do not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals may be obtained by contacting the sponsor, Merck Canada Inc. at: 1-800-567-2594.

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