PRODUCT MONOGRAPH

PrPRZ-OLMESARTAN

Olmesartan Medoxomil Tablets, USP

20 mg, and 40 mg

Angiotensin II AT_1 Receptor Blocker

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PrPRZ-OLMESARTAN

Olmesartan Medoxomil Tablets
20 mg and 40 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet / 20 mg, and 40 mg	Hypromellose, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, talc, and titanium dioxide

INDICATIONS AND CLINICAL USE

PRZ-OLMESARTAN (olmesartan medoxomil) is indicated for the treatment of mild to moderate essential hypertension.

PRZ-OLMESARTAN may be used alone or in combination with thiazide diuretic.

Geriatrics (≥65 years of age):
No overall differences in effectiveness or safety were observed between elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between these subjects, however, greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (6–16 years of age):
Antihypertensive effects of olmesartan medoxomil have been demonstrated in hypertensive pediatric patients aged 6 to 16 years. Use of olmesartan medoxomil in this age group is supported by evidence from an adequate and well-controlled study of olmesartan medoxomil in pediatric patients (see **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS, Special Populations, ACTION AND CLINICAL PHARMACOLOGY**, and **CLINICAL TRIALS**).

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.

- Concomitant use of angiotensin receptor antagonists (ARBs) including PRZ-OLMESARTAN with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR<60 mL/min/1.73 m^2) is contraindicated (see **WARNINGS AND PRECAUTIONS, Dual Blockade of the**

Renin-Angiotensin System (RAS) and Renal, and **DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, PRZ-OLMESARTAN (olmesartan medoxomil) 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- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with PRZ-OLMESARTAN. 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**). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

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.

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as olmesartan mexdoxomil, or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR<60 mL/min/1.73 m^2). Therefore, the use of PRZ-OLMESARTAN in combination with aliskiren-containing drugs is contraindicated in these patients (see **CONTRAINDICATIONS**). Further, co-administration of ARBs, including PRZ-OLMESARTAN, with other agents blocking the RAS, such as ACEIs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure and hyperkalemia.

Endocrine and Metabolism

PRZ-OLMESARTAN contains olmesartan, a drug that inhibits the renin-angiotensin system (RAS). Drugs that inhibit the RAS can cause hyperkalaemia. Monitor serum electrolytes

periodically.

Gastrointestinal

Sprue-like Enteropathy: Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan and no other etiology is identified, discontinue PRZ-OLMESARTAN.

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 olmesartan medoxomil 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 PRZ-OLMESARTAN in this group of patients is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Renal

Impaired Renal Function: as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. 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, progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations**).

The use of ARBs – including PRZ-OLMESARTAN or ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR<60 mL/min/1.73 m^2) (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs**).

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.

Use of olmesartan medoxomil should include appropriate assessment of renal function.

Sensitivity/Resistance

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

Special Populations

It is not recommended for women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraceptive measures to take PRZ-OLMESARTAN (see boxed text above).

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, PRZ-OLMESARTAN should be discontinued as soon as possible.

The use of ARB 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, hyperkalaemia).

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.

Animal Data

No teratogenic effects were observed when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1000 mg/kg/day (240 times the maximum recommended human dose [MRHD] of olmesartan medoxomil on a mg/m^2 basis) pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m2 basis; higher doses could not be evaluated for effects on fetal development as they were lethal to the does). In rats, significant decreases in pup birth weight and weight gain were observed at doses ≥1.6 mg/kg/day, and delays in developmental milestones and dose-dependent increases in the incidence of dilation of the renal pelvis were observed at doses ≥8 mg/kg/day. The no observed effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

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. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, 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 (6–16 years of age): the antihypertensive effect of olmesartan medoxomil was evaluated in one randomized, double-blind dose-response study of a limited duration of 3 weeks in pediatric patients 6 to 16 years of age. The clinical trial also included a 46-week open-label extension period that showed maintenance of the blood pressure lowering effects (see **CLINICAL TRIALS**). The pharmacokinetics of olmesartan medoxomil were evaluated in pediatric patients 6 to 16 years of age (see **ACTION AND CLINICAL PHARMACOLOGY**). Olmesartan medoxomil was generally well tolerated in pediatric patients, and the adverse experience profile was similar to that described for adults.

There are no data on the effect of olmesartan medoxomil on blood pressure in neonates and pediatric patients with malignant hypertension.

Children <1 year of age must not receive PRZ-OLMESARTAN for hypertension. Drugs that act directly on the renin-angiotensin-aldosterone-system (RAAS) can affect the development of immature kidneys.

There are very limited data on the effect of olmesartan medoxomil in pediatric patients 1–5 years of age.

Renal impairment: There are very limited data on the effect of olmesartan medoxomil on blood pressure in pediatric patients with renal impairment.

Hepatic impairment: There are no data on the effect of olmesartan medoxomil in pediatric patients with hepatic impairment.

Geriatrics (≥65 years of age): no overall differences in effectiveness or safety were observed between elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between these subjects, however, greater sensitivity of some older individuals cannot be ruled out (see **CLINICAL TRIALS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adults:
Olmesartan medoxomil has been evaluated for safety in 3825 patients/subjects treated for essential hypertension, including 900 patients treated for at least 6 months and more than 525 for at least 1 year. Of these, 3275 patients were treated with olmesartan medoxomil monotherapy in controlled clinical trials.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences occurred in 2.4% (79/3278) and 2.7% (i.e. 32/1179) of patients treated with olmesartan medoxomil and placebo or active control, respectively.

Treatment with olmesartan medoxomil was well tolerated, with an incidence of adverse events

similar to placebo. Events generally were mild, transient and had no relationship to the dose of olmesartan medoxomil. The following potentially serious adverse reactions have been reported with olmesartan medoxomil / combined olmesartan medoxomil and hydrochlorothiazide in controlled trials: syncope, hypotension.

Pediatrics (6–16 years of age):
No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.

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 double-blind placebo-controlled clinical trials, the following adverse events were reported with olmesartan medoxomil occurring in >1% of patients, irrespective of relationship to study drug.

Table 1: Adverse Events Occurring >1% in Placebo-controlled Monotherapy Studies[a]

System Organ Class (SOC)	Placebo		Total Olmesartan Medoxomil	
	N=555		N=2540	
MedDRA Preferred term	N	%	N	%
Gastrointestinal disorders				
Diarrhea	4	(0.7)	27	(1.1)
General disorders and administration site conditions				
Influenza like illness	16	(2.9)	79	(3.1)
Infections and Infestations				
Upper respiratory tract infection	27	(4.9)	83	(3.3)
Bronchitis	10	(1.8)	51	(2.0)
Rhinitis	9	(1.6)	40	(1.6)
Pharyngitis	6	(1.1)	33	(1.3)
Sinusitis	11	(2.0)	29	(1.1)
Injury, poisoning and procedural complications				
Injury	7	(1.3)	34	(1.3)
Metabolism and connective tissue				
Hyperglycemia	15	(2.7)	32	(1.3)
Hypertriglyceridemia	6	(1.1)	29	(1.1)
Musculoskeletal and connective tissue disorders				
Back pain	8	(1.4)	41	(1.6)
Nervous system disorders				
Headache	40	(7.2)	141	(5.6)
Dizziness	5	(0.9)	70	(2.8)

Table 1: Adverse Events Occurring >1% in Placebo-controlled Monotherapy Studies[a]				
System Organ Class (SOC)	**Placebo**		**Total Olmesartan Medoxomil**	
	N=555		N=2540	
MedDRA Preferred term	N	%	N	%
Renal and urinary disorders				
Hematuria	10	(1.8)	49	(1.9)

[a] Body systems in which patients in either treatment group experienced events and in which at least one event was reported in >1% of patients in either treatment group.

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

Other (potentially important) adverse events that have been reported in controlled or open-label trials with an incidence of greater than 0.5%, regardless of causality:

Cardiac disorders: tachycardia.
Ear and labyrinth disorders: vertigo.
Gastrointestinal disorders: abdominal pain, dyspepsia, nausea.
General disorders and administration site conditions: chest pain, edema peripheral.
Infections and infestations: gastroenteritis.
Metabolism and nutrition disorders: hypercholesterolemia, hyperlipidemia, hyperuricaemia.
Musculoskeletal and connective tissue disorders: arthralgia, arthritis, myalgia.
Renal and urinary disorders: albuminuria.
Respiratory, thoracic and mediastinal disorders: cough.
Skin and subcutaneous tissue disorders: rash.

Facial edema was reported in 5 patients receiving olmesartan medoxomil. Angioedema has been reported with other angiotensin II 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.

Hemoglobin and Hematocrit: small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g/dL and 0.3 volume percent, respectively) were observed.

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

	Placebo (n=555)	Total Olmesartan Medoxomil (n=2450)
γGT increased	13 (2.3%)	57 (2.2%)
CPK increased	6 (1.1%)	40 (1.6%)
ALT increased	9 (1.6%)	33 (1.3%)
AST increased	6 (1.1%)	25 (1.0%)

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, blood uric acid increased and sprue-like enteropathy.

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

In the Randomised Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) clinical study including 4447 patients with type 2 diabetes, normo-albuminuria and at least one additional cardiovascular risk factor, cardiovascular events occurred in 96 patients (4.3%) with olmesartan and in 94 patients (4.2%) with placebo. The incidence of cardiovascular mortality was higher with olmesartan compared to placebo treatment (15 patients (0.66%) vs. 3 patients (0.14%) [HR=4.94; 95% CI=1.43–17.06]). The patient population at increased risk had pre-existing coronary artery disease.

DRUG INTERACTIONS

Drug-Drug Interactions

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 PRZ-OLMESARTAN. The possibility of symptomatic hypotension with the use of PRZ-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.

Agents Increasing Serum Potassium

Since olmesartan medoxomil 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. Potassium-containing salt substitutes should also be used with caution.

Pravastatin

Olmesartan medoxomil decreased the C_{max} and AUC of pravastatin by approximately 25% and 21%, respectively. Since there is a high degree of variability in the bioavailability of pravastatin, this finding is not considered to be clinically relevant.

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.

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.

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.

Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs
Dual Blockade of the Renin-Angiotensin-System with ARBs, ACEIs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in any other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure and hyperkalemia. See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS)**.

Drug-Food Interactions
PRZ-OLMESARTAN 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

- **Elderly:** no adjustment of dosage is generally required in elderly patients (see below for dose recommendations 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).

- **Pediatrics (6–16 years of age):** Dosage must be individualized. The usual recommended starting dose of PRZ-OLMESARTAN is 10 mg once daily for patients who weigh 20 to <35 kg, or 20 mg once daily for patients who weigh ≥35 kg. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of PRZ-OLMESARTAN may be increased to a maximum of 20 mg once daily for patients who weigh 20 to <35 kg or 40 mg once daily for patients who weigh ≥35 kg.

- **Hepatic Impairment:**
  Adults: 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 olmesartan medoxomil 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 PRZ-OLMESARTAN in this group of patients is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

  Pediatrics (6–16 years of age): There are no data on the effect of olmesartan medoxomil in pediatric patients with hepatic impairment; therefore, use of PRZ-OLMESARTAN in this group of patients is not recommended.

- **Renal Impairment:**
  Adults: Owing to 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.

  Pediatrics (6–16 years of age): There are very limited data on the effect of olmesartan medoxomil on blood pressure in pediatric patients with renal impairment; therefore, use of PRZ-OLMESARTAN in this group of patients is not recommended.

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

Recommended Dose and Dosage Adjustment

Dosage must be individualized.

Adults:

The usual recommended starting dose of PRZ-OLMESARTAN (olmesartan medoxomil) is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of PRZ-OLMESARTAN may be increased to 40 mg. Doses above 40 mg do not appear to have greater

effect. Twice-daily dosing offers no advantage over the same total dose given once daily.

Pediatrics (6–16 years of age):
See **DOSAGE AND ADMINISTRATION, Dosing Considerations, Pediatrics (6–16 years of age).**

PRZ-OLMESARTAN may be administered with or without food.

Concomitant Diuretic Therapy
If blood pressure is not controlled by PRZ-OLMESARTAN alone, a thiazide diuretic may be added.

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.

Limited data are available in regard 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.

ACTION AND CLINICAL PHARMACOLOGY

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

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

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

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan 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.

Pharmacodynamics

Olmesartan medoxomil inhibits the pressor effect of an angiotensin II infusion in a dose-dependent manner at doses of 2.5 to 40 mg. The inhibition was 90% at doses of olmesartan medoxomil >40 mg 24 hours post dose.

Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increased 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.

Pharmacokinetics

Absorption: 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.

Distribution: 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.

Metabolism and Excretion: following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

Special Populations and Conditions

Pediatrics (6–16 years of age): The pharmacokinetics of olmesartan were studied in pediatric hypertensive patients aged 6 to 16 years. The clearance of olmesartan in pediatric patients was

similar to that in adult patients when adjusted by the body weight.

Geriatrics (≥65 years of age): the pharmacokinetics of olmesartan was studied in the elderly (≥65 years). Overall, maximum plasma concentrations of olmesartan were similar in young adults and the elderly. Modest 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, theclinical 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 adult and pediatric (6–16 years of age) 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} 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 controlled room temperature between 15°C and 30°C in a tight container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DOSAGE FORM: PRZ-OLMESARTAN (olmesartan medoxomil) is available as film-coated tablets:

Olmesartan Medoxomil Tablets 20 mg: White round shaped, film coated tablets, debossed with "OLM" on one side and "20" on other side.

Olmesartan Medoxomil Tablets 40 mg: White oval shaped, film coated tablets, debossed with "OLM" on one side and "40" on other side.

COMPOSITION: PRZ-OLMESARTAN contains 20 mg or 40 mg of olmesartan medoxomil and non-medicinal ingredients: hypromellose, hydroxypropyl cellulose, lactose monohydrate, low-substituted Hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, talc, and titanium dioxide.

PACKAGING:
Bottle packs of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

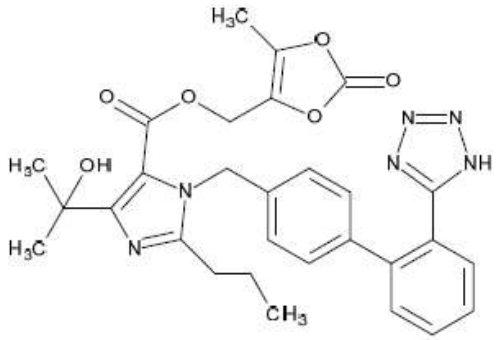
Drug Substance

Proper name: olmesartan medoxomil

Chemical name: 1H-imidazole-5-carboxylic acid, 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4yl]methyl]-,(5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester

Molecular formula and molecular mass: $C_{29}H_{30}N_6O_6$
558.6 g/mol

Structural formula:



Physicochemical properties: Olmesartan medoxomil is a white or almost white crystalline powder. It is slightly soluble in ethanol (96%) and practically insoluble in water and heptane.

The dissociation constant (pKa) of olmesartan medoxomil was determined to be 0.91 and 5.57.

CLINICAL TRIALS

Comparative Bioavailability Study

A double blind, randomized, two-period, two-treatment, two-sequence, crossover, single dose oral bioequivalence study comparing PRZ-OLMESARTAN tablets, 40 mg (Pharmaris Canada Inc.) to [Pr]OLMETEC® tablets, 40 mg (Merck Canada Inc.) was conducted in 36 healthy adult Asian male subjects under fasting conditions. A summary of the data from 36 subjects who completed the study is presented in the following table.

Olmesartan (1 x 40mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Interval
AUC_T (ng*hr/mL)	8380.95 8846.90 (36.01)	7750.12 8130.67 (32.17)	108.1	101.0 - 115.8
AUC_I (ng*hr/mL)	8766.61 9230.06 (35.39)	8107.83 8476.80 (31.16)	108.1	101.6 - 115.1
C_{max} (ng/mL)	1301.57 1338.31 (24.81)	1174.03 1218.06 (26.60)	110.9	102.9 - 119.5
T_{max}§ (h)	2.00 (1.00 - 3.33)	2.17 (1.00 - 3.67)		
$T_{½}$€ (h)	6.93 (29.60)	6.98 (28.66)		

* PRZ-OLMESARTAN tablets, 40 mg (Pharmaris Canada Inc.).
† PrOLMETEC® tablets, 40 mg (Merck Canada Inc.) were purchased in Canada.
§ Expressed as the median (range) only.
€ Expressed as the arithmetic mean (CV %) only.

Study Results

Adults

Study demographics and trial design
The antihypertensive effects of olmesartan medoxomil have been demonstrated in seven double-blind, placebo-controlled, parallel-group studies at doses ranging from 2.5 to 80 mg for 6 to 12 weeks. A total of 548 patients received placebo and 2145 patients received olmesartan medoxomil. The percent of patients treated with olmesartan medoxomil in each of the dose groups were 13.1% (2.5 mg), 27.9% (5 mg), 20.8% (10 mg), 20.3% (20 mg), 9.1% (40 mg), and 8.8% (80 mg). In the placebo group, 56.8% were male and 43.2% were female, and in the combined olmesartan medoxomil group, 51.9% were male and 48.1% were female. In the placebo and combined olmesartan medoxomil groups 88.5% and 91.1% of patients respectively, were Caucasian. The mean age of the patients was 55.2 years in the placebo group and 55.7 years in the combined olmesartan medoxomil group. Approximately 80% of patients were under 65 years of age and approximately 20% were 65 years of age or older.

Study results
In the placebo-controlled studies, a total of 2693 patients with mild to moderate essential hypertension were studied. The primary efficacy parameter was the change from baseline in trough sitting DBP at the primary time points (week 6, week 8, or week 12). olmesartan medoxomil once daily (QD) was shown to lower systolic and diastolic blood pressure. The response was dose- related. An olmesartan medoxomil dose of 20 mg daily produced a trough sitting placebo adjusted systolic and diastolic blood pressure reduction of about 10 and 6 mmHg,

respectively (P<0.001) and a dose of 40 mg daily produced a trough sitting BP reduction over placebo of about 12/7 mmHg (P<0.001). Olmesartan medoxomil doses greater than 40 mg had little additional effect. The onset of the antihypertensive effect occurred within 1 week and was largely manifested 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 and safety 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.

When hydrochlorothiazide treatment was added, the resulting decrease in blood pressure was larger than the one induced by each component individually.

Pediatrics

The antihypertensive effects of olmesartan medoxomil in the pediatric population were evaluated in a randomized, double-blind dose-response study involving 302 hypertensive patients aged 6 to 16 years. The study population consisted of an all Black cohort of 112 patients and a mixed racial cohort of 190 patients, including 38 Blacks. The etiology of the hypertension was predominantly essential hypertension (87% of the Black cohort and 67% of the mixed cohort). Patients who weighed 20 to <35 kg were randomized to 2.5 (low dose) or 20 (high dose) mg of olmesartan medoxomil once daily and patients who weighed ≥35 kg were randomized to 5 (low dose) or 40 (high dose) mg of olmesartan medoxomil once daily. At the end of 3 weeks, patients were re-randomized to continuing olmesartan medoxomil or placebo for up to 2 weeks. During the initial 3-week dose-response phase, olmesartan medoxomil significantly reduced both systolic and diastolic blood pressure in a weight-adjusted dose-dependent manner. Overall, the low and high dose levels of olmesartan medoxomil significantly reduced systolic blood pressure by 6.6 and 11.9 mmHg from baseline, respectively, and diastolic blood pressure by 4.8 and 8.8 mmHg from baseline, respectively. These reductions in systolic and diastolic blood pressure included both drug and placebo effect. During the randomized withdrawal to placebo phase, mean systolic and diastolic blood pressure at trough were 3.2 and 2.8 mmHg lower, respectively, in patients continuing olmesartan medoxomil than in patients withdrawn to placebo. These differences were statistically different. As observed in adult populations, the blood pressure reductions were smaller in Black patients.

DETAILED 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 AT_1 receptor, with negligible binding to the AT_2 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.

The inhibitory effect of olmesartan on the AII pressor response in rats is independent of cytochrome P450 metabolism.

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.

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.

Carcinogenicity

Oncogenicity studies demonstrated that olmesartan medoxomil was not carcinogenic when administered at doses up to 2000 mg/kg/day in 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.

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.

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Product Monograph, OLMETEC®, Merck Canada Inc., Date of Revision: December 01, 2016. Control #198091.

PART III: CONSUMER INFORMATION

PrPRZ-OLMESARTAN
(Olmesartan Medoxomil tablets)
20 mg and 40 mg

Read this carefully before you start taking PRZ-OLMESARTAN and each time you get a refill. This leaflet is a summary and will not tell you everything about PRZ-OLMESARTAN. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about PRZ-OLMESARTAN.

ABOUT THIS MEDICATION

What the medication is used for:
PRZ-OLMESARTAN is used to lower blood pressure in adults and children above 6 years old.

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:
PRZ-OLMESARTAN contains a drug olmesartan medoxomil which acts to inhibit the naturally occurring hormone, angiotensin II in the human body that causes the blood vessels to constrict. As an angiotensin receptor blocker (ARB), PRZ-OLMESARTAN lowers blood pressure by relaxing the blood vessels and as a result blood pressure is lowered. You can recognize an ARB because its medicinal ingredient ends in "SARTAN".

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking PRZ-OLMESARTAN regularly even if you feel fine.

When it should not be used:
Do not take PRZ-OLMESARTAN if you:
- Are allergic to Olmesartan medoxomil or to any non-medicinal ingredient in the formulation.
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat,or sudden difficulty breathing or swallowing, to any ARB. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Are pregnant or intend to become pregnant. If this is the case, talk to your doctor as soon as possible. Taking PRZ-OLMESARTAN during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. It is possible that PRZ-OLMESARTAN passes into breast milk.
- Are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.

PRZ-OLMESARTAN is not recommended for use in children below the age of 6 years.

What the medicinal ingredient is:
Olmesartan medoxomil

What the nonmedicinal ingredients are: Hypromellose, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, talc, and titanium dioxide.

What dosage forms it comes in:
Film-Coated Tablets: 20 mg (white, round shaped) and 40 mg (white, oval shaped).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
PRZ-OLMESARTAN should not be used during pregnancy. If you discover that you are pregnant while taking PRZ-OLMESARTAN, stop the medication and **please contact your doctor, nurse, or pharmacist as soon as possible.**

BEFORE you use PRZ-OLMESARTAN talk to your doctor or pharmacist if you:
- have experienced an allergic reaction to any drug used to lower blood pressure.
- have narrowing of a heart valve, heart or blood vessel disease.
- have diabetes, liver or kidney disease.
- are on dialysis.
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- are on a low-salt diet.
- are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill" that makes your body keep potassium).
- are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with PRZ-OLMESARTAN is not recommended.
- are taking an angiotensin converting enzyme inhibitor (ACEI). You can recognize ACEIs because their medicinal ingredient ends in "**-PRIL**".
- are less than 18 years old.

PRZ-OLMESARTAN can cause severe chronic diarrhea with substantial weight loss (sprue-like enteropathy). It can take months to years for symptoms to develop.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to PRZ-OLMESARTAN. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with PRZ-OLMESARTAN:
- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Blood pressure lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), or angiotensin coverting enzyme inhibitors (ACEIs).
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib (COX-2 Inhibitor).

PROPER USE OF THIS MEDICATION

Usual dose:

For adult patients: 20 mg tablet once daily. It can be increased to 40 mg by your doctor if your blood pressure is not well controlled.

For pediatric patients age 6 to 16 of age:
Children weight between 20 kg to less than 35 kg: 10 mg once daily. If the blood pressure is not well controlled, your doctor can double the dosage to 20 mg once daily.

Children weight 35 kg or more: 20 mg once daily.

If the blood pressure is not well controlled, your doctor can double the dosage to 40 mg once daily.

PRZ-OLMESARTAN may be taken with or without food.

Overdose:

If you think you have taken too much PRZ-OLMESARTAN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unintended or undesirable effects, so-called side effects.

Side effects may include:
- dizziness
- drowsiness, insomnia
- rash
- diarrhea, vomiting
- headache
- bronchitis
- back or leg pain, muscle pain and cramps
- upper respiratory tract infection

If any of these affects you severely, tell your doctor, nurse or pharmacist.

PRZ-OLMESARTAN can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness.	√		
	Increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell.		√	
Uncommon	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			√
	Rhabdomyolysis: muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine.		√	
	Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue.		√	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		√	

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
		Only if severe	**In all cases**	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms.		√	
	Decreased Platelets: bruising, bleeding, fatigue and weakness.		√	
Unknown	**Sprue-like enteropathy:** severe chronic diarrhea with substantial weight loss.		√	

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

HOW TO STORE IT

Stored at controlled room temperature between 15°C and 30°C in a tight container.
Keep out of sight and reach of children and pets.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about PRZ-OLMESARTAN:

- Talk with your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information Section by vising the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.pharmaris.com, or by calling 1-866-913-7955.

This leaflet was prepared by Pharmaris Canada Inc.

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