

## PRODUCT MONOGRAPH

Pr **OLMETEC**<sup>®</sup>

Olmesartan Medoxomil

5 mg, 20 mg, and 40 mg Tablets

Angiotensin II AT<sub>1</sub> Receptor Blocker

Merck Canada Inc.  
16750, route Transcanadienne  
Kirkland, Québec H9H 4M7

Date of Preparation:  
August 18, 2011

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Submission Control No: 147971

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**Pr<sup>o</sup>OLMETEC<sup>®</sup>**  
**Olmesartan Medoxomil**

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Nonmedicinal Ingredients</b>
Oral	Tablet / 5 mg, 20 mg, and 40 mg	hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide, and yellow iron oxide (5 mg only)

**INDICATIONS AND CLINICAL USE**

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

OLMETEC 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 (< 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.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT<sub>1</sub>) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, OLMETEC (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 OLMETEC. 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.

### 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 OLMETEC 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**).

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**

**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 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, 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.

### 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<sup>2</sup> basis) pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m<sup>2</sup> 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  $\geq$  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  $\geq$  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 (< 18 years of age):** the safety and effectiveness in pediatric patients have not been established.

**Geriatrics ( $\geq$  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

OLMETEC (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 OLMETEC and placebo or active control, respectively.

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

**Table 1: Adverse Events Occurring > 1% in Placebo-controlled Monotherapy Studies<sup>a</sup>**

System Organ Class (SOC)  MedDRA Preferred term	Placebo N=555		Total Olmesartan Medoxomil N=2540	
	N	%	N	%
<b>Gastrointestinal disorders</b>				
Diarrhea	4	(0.7)	27	(1.1)
<b>General disorders and administration site conditions</b>				
Influenza like illness	16	(2.9)	79	(3.1)
<b>Infections and Infestations</b>				
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)
<b>Injury, poisoning and procedural complications</b>				
Injury	7	(1.3)	34	(1.3)
<b>Metabolism and nutrition disorders</b>				
Hyperglycemia	15	(2.7)	32	(1.3)
Hypertriglyceridemia	6	(1.1)	29	(1.1)
<b>Musculoskeletal and connective tissue disorders</b>				
Back pain	8	(1.4)	41	(1.6)
<b>Nervous system disorders</b>				
Headache	40	(7.2)	141	(5.6)
Dizziness	5	(0.9)	70	(2.8)
<b>Renal and urinary disorders</b>				
Hematuria	10	(1.8)	49	(1.9)

<sup>a</sup>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.

	<u>Placebo</u> (n=555)	<u>Total Olmesartan Medoxomil</u> (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, and blood uric acid increased.

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

## **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 OLMETEC. The possibility of symptomatic hypotension with the use of OLMETEC 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 OLMETEC 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**

OLMETEC decreased the C<sub>max</sub> 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 OLMETEC (olmesartan medoxomil) in healthy volunteers.

#### **Digoxin**

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

#### **Antacids**

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

#### **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.

### **Drug-Food Interactions**

OLMETEC 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**).
- **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 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 OLMETEC in this group of patients is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).
- **Renal Impairment:** 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.

- For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), OLMETEC 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.

The usual recommended starting dose of OLMETEC (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 OLMETEC 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.

OLMETEC may be administered with or without food.

### **Concomitant Diuretic Therapy**

If blood pressure is not controlled by OLMETEC 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.
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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<sub>1</sub> 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<sub>1</sub> receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT<sub>2</sub> 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<sub>1</sub> receptor than for the AT<sub>2</sub> 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<sub>max</sub>) 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 (< 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 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, 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  $C_{max}$  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 (olmesartan medoxomil) is available as film-coated tablets.

COMPOSITION: OLMETEC contains 5 mg (yellow, round shaped), 20 mg (white, round shaped), or 40 mg (white, oval-shaped) of olmesartan medoxomil. The inactive ingredients in OLMETEC are: hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide, and yellow iron oxide (5 mg only). Tablets are debossed with C12, C14, or C15 on one side of the 5, 20, and 40 mg tablets, respectively.

### **PACKAGING:**

5 mg: 30 tablets per bottle.

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

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

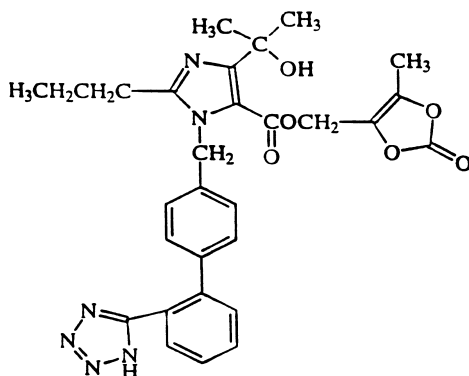
#### Drug Substance

Common 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]-4-yl]methyl]-,(5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester

Molecular formula and molecular mass:  $C_{29}H_{30}N_6O_6$   
558.59

Structural formula:



Physicochemical properties: Olmesartan medoxomil is a white to pale yellowish-white powder. It is practically insoluble in water and sparingly soluble in methanol.

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).

## CLINICAL TRIALS

### Study demographics and trial design

The antihypertensive effects of OLMETEC (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 OLMETEC. The percent of patients treated with OLMETEC 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 OLMETEC group, 51.9% were male and 48.1% were female. In the placebo and combined OLMETEC 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 OLMETEC 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). OLMETEC 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 mm Hg ( $p < 0.001$ ). 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 OLMETEC once daily, with trough-to-peak ratios for systolic and diastolic response between 60 and 80%.

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

The antihypertensive effect and safety of OLMETEC 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.

## 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<sub>1</sub> receptor, with negligible binding to the AT<sub>2</sub> 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 ( $\geq 1700$  mg/kg) and rats ( $\geq 1400$  mg/kg) with lethality in mice at  $\geq 1850$  mg/kg and at  $\geq 1550$  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<sup>2</sup> 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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## PART III: CONSUMER INFORMATION

### Pr OLMETEC® (Olmesartan Medoxomil)

This leaflet is part III of a three-part “Product Monograph” published when OLMETEC 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. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

OLMETEC is used to lower blood pressure.

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 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. OLMETEC lowers blood pressure by specifically blocking the action of angiotensin II, and thus relaxing the blood vessels and as a result blood pressure is lowered.

##### When it should not be used:

You should not take OLMETEC if you:

- are pregnant or plan to become pregnant. If this is the case, talk to your doctor as soon as possible.
- are breastfeeding.
- are allergic to olmesartan medoxomil or to any other component of this product.

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

##### What the medicinal ingredient is:

Olmesartan medoxomil

##### What the nonmedicinal ingredients are:

Hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide, and yellow iron oxide (5 mg only).

##### What dosage forms it comes in:

Film-Coated Tablets: 5 mg (yellow, round shaped), 20 mg (white, round shaped), 40 mg (white, oval shaped).

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

OLMETEC should not be used during pregnancy.

If you discover that you are pregnant while taking OLMETEC, stop the medication and please contact your physician.

### BEFORE you use OLMETEC 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.
- 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.

If OLMETEC 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 to lower your blood pressure. This means that OLMETEC 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 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, contact immediately your doctor.

It is possible that OLMETEC passes into breast milk. You should discuss with your doctor about taking OLMETEC 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 include:

- Medicines used to lower blood pressure, including diuretics (water pills)
- Potassium-sparing diuretics (potassium supplements or salt substitutes containing potassium)
- Lithium salts
- Medicines used to reduce pain and swelling called Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and COX-2 Inhibitors

**PROPER USE OF THIS MEDICATION**

**Usual dose:**

The initial recommended dose is one 20 mg tablet once a day. If your blood pressure is not well controlled, your doctor may increase the dose to 40 mg, and/or decide to add another medicine (e.g. a thiazide diuretic).

OLMETEC 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 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, some may experience dizziness, headache, bronchitis, back pain, diarrhea, or 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	
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)			√
	Allergic Reactions (rash, swelling of the lips, face or neck, difficulty breathing or speaking)			√
Very rare	Hypotension (dizziness or light-headedness including fainting may occur due to low blood pressure)			√
	Dark/brown urine		√	
	Muscle pain		√	
	Bronchitis (shortness of breath, weakness, high fever, coughing and fatigue)		√	

*This is not a complete list of side effects. For any unexpected effects while taking OLMETEC, 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:**

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- **Report online at [www.healthcanada.gc.ca/medeffect](http://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](http://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.

This leaflet was prepared by Merck Canada Inc.  
Last revised: August 18, 2011

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