

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr APO-OLMESARTAN

Olmesartan Medoxomil Tablets

20 mg and 40 mg, Oral

USP

Angiotensin II AT₁ Receptor Blocker

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T9

Date of Initial Authorization:
May 01, 2017

Date of Revision:
August 3, 2022

Submission Control Number: 261965

RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS, Pregnancy and Breastfeeding	08/2022
7 Warnings and Precautions, 7.1 Special Populations, 7.1.1 Pregnant women	08/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics.....	4
1.2 Geriatrics.....	4
2 CONTRAINDICATIONS	4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	5
4 DOSAGE AND ADMINISTRATION	5
4.1 Dosing Considerations.....	5
4.2 Recommended Dose and Dosage Adjustment.....	6
4.3 Reconstitution	6
4.4 Administration.....	6
4.5 Missed Dose	6
5 OVERDOSAGE	7
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	7
7 WARNINGS AND PRECAUTIONS	7
7.1 Special Populations	9
7.1.1 Pregnant Women.....	9
7.1.2 Breast-feeding	10
7.1.3 Pediatrics (6 to 16 years of age).....	11
7.1.4 Geriatrics (≥ 65 years of age)	11
8 ADVERSE REACTIONS	11
8.1 Adverse Reaction Overview.....	11
8.2 Clinical Trial Adverse Reactions	12
8.3 Less Common Clinical Trial Adverse Reactions (<1%)	13

8.4	Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.....	13
8.5	Clinical Trial Adverse Reactions (Pediatrics)	14
8.6	Post-Market Adverse Reactions.....	14
9	DRUG INTERACTIONS	14
9.1	Serious Drug Interactions.....	14
9.2	Overview	14
9.3	Drug-Drug Interactions.....	15
9.4	Drug-Food Interactions	18
9.5	Drug-Herb Interactions.....	18
9.6	Drug-Laboratory Test Interactions	18
9.7	Drug-Lifestyle Interactions	18
10	CLINICAL PHARMACOLOGY.....	18
10.1	Mechanism of Action	18
10.2	Pharmacodynamics.....	19
10.3	Pharmacokinetics.....	19
11	STORAGE, STABILITY AND DISPOSAL	21
12	SPECIAL HANDLING INSTRUCTIONS.....	21
PART II: SCIENTIFIC INFORMATION		22
13	PHARMACEUTICAL INFORMATION.....	22
14	CLINICAL TRIALS	23
14.1	Trial Design and Study Demographics.....	23
14.2	Study Results.....	23
14.3	Comparative Bioavailability Studies.....	25
15	MICROBIOLOGY	25
16	NON-CLINICAL TOXICOLOGY.....	26
17	SUPPORTING PRODUCT MONOGRAPHS.....	27
PATIENT MEDICATION INFORMATION		28

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

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

1.1 Pediatrics

Pediatrics (6 to 16 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of olmesartan medoxomil in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use. 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 [2 CONTRAINDICATIONS](#), [7 WARNINGS AND PRECAUTIONS](#), [7.1 Special Populations](#), [10 CLINICAL PHARMACOLOGY](#) and [14 CLINICAL TRIALS](#)).

1.2 Geriatrics

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.

2 CONTRAINDICATIONS

APO-OLMESARTAN is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see the [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#) section of the product monograph.

- Concomitant use of angiotensin receptor antagonists (ARBs) including APO-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 m²) is contraindicated (see [7 WARNINGS AND PRECAUTIONS](#), [Dual Blockade of the Renin-Angiotensin System \(RAS\)](#) and [Renal](#) and [9 DRUG INTERACTIONS](#), [Dual Blockade of the Renin Angiotensin System \(RAS\) with ARBs, ACE inhibitors or aliskiren-containing drugs](#)).
- Pregnant women (see [7 WARNINGS AND PRECAUTIONS](#), [7.1 Special Populations](#), [7.1.1 Pregnant Women](#))
- Breastfeeding women (see [7 WARNINGS AND PRECAUTIONS](#), [7.1 Special Populations](#),

[7.1.2 Breastfeeding\)](#)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT₁) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, APO-OLMESARTAN (olmesartan medoxomil) should be discontinued as soon as possible (see [7 WARNINGS AND PRECAUTIONS](#), [7.1 Special Populations](#)).

4 DOSAGE AND ADMINISTRATION

4.1 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 [10 CLINICAL PHARMACOLOGY](#), [10.3 Pharmacokinetics](#), [Special Populations and Conditions](#)).
- **Pediatrics (6 to 16 years of age):** Dosage must be individualized. The usual recommended starting dose of APO-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 APO-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 APO-OLMESARTAN in this group of patients is not recommended (see [10 CLINICAL PHARMACOLOGY](#), [10.3 Pharmacokinetics](#)).

Pediatrics (6 to 16 years of age): There are no data on the effect of olmesartan medoxomil in pediatric patients with hepatic impairment; therefore, use of APO-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 to 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 APO-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), APO-OLMESARTAN should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see [7 WARNINGS AND PRECAUTIONS, Renal](#)).

4.2 Recommended Dose and Dosage Adjustment

Dosage must be individualized.

Adults:

The usual recommended starting dose of APO-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 APO-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 to 16 years of age):

See [4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations, Pediatrics \(6 to 16 years of age\)](#).

Concomitant Diuretic Therapy

If blood pressure is not controlled by APO-OLMESARTAN alone, a thiazide diuretic may be added.

4.3 Reconstitution

Not applicable

4.4 Administration

APO-OLMESARTAN may be administered with or without food

4.5 Missed Dose

If patients miss a dose, they should wait until their next scheduled dose. Patients should

not double their dose.

5 OVERDOSAGE

Limited data are available in regard to overdose in humans. The most likely manifestations of overdose 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	All non-medicinal Ingredients
Oral	Tablet (film-coated)/20 mg, and 40 mg	hydroxypropyl cellulose, hypromellose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, purified talc, and titanium dioxide.

COMPOSITION: APO-OLMESARTAN contains 20 mg (white to off white, round, biconvex), or 40 mg (white to off white, oval, biconvex) of olmesartan medoxomil. The non-medicinal ingredients in APO-OLMESARTAN are: hydroxypropyl cellulose, hypromellose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, purified talc, and titanium dioxide. Tablets are debossed with “FS2” or “FS3” on one side of 20, and 40 mg tablets, respectively and are plain on the other side.

PACKAGING:

20 mg and 40 mg: Bottle of 90 tablets

7 WARNINGS AND PRECAUTIONS

Please see the [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#) at the beginning of Part I: Health Professional Information.

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 APO-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 [4 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 medoxomil, or of angiotensin-converting-enzyme inhibitors (ACE) inhibitors 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 m²). Therefore, the use of APO-OLMESARTAN in combination with aliskiren-containing drugs is contraindicated in these patients (see [2 CONTRAINDICATIONS](#)). Further, co-administration of ARBs, including olmesartan medoxomil, with other agents blocking the RAS, such as ACE inhibitors 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

APO-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 APO-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 APO-OLMESARTAN in this group of patients is not recommended (see [10 CLINICAL PHARMACOLOGY, 10.3 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 [10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and conditions](#)).

The use of ARBs – including APO-OLMESARTAN or ACE inhibitors with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 mL/min/1.73 m²) (see [2 CONTRAINDICATIONS](#) and [9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System \(RAS\) with ARBs, ACE Inhibitors 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.

7.1 Special Populations

APO-OLMESARTAN is contraindicated for women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraceptive measures to take APO-OLMESARTAN (see [boxed warning](#) above and section [7.1.1 Pregnant Women](#)).

7.1.1 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, APO-OLMESARTAN should be discontinued as soon as possible. If APO-OLMESARTAN is used during pregnancy, or if the patient becomes pregnant while taking APO-OLMESARTAN, the patient should be apprised of the potential hazard to a fetus.

The use of ARB is contraindicated during pregnancy. 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). Should exposure to APO-OLMESARTAN have occurred from the second trimester forward, ultrasound examinations of the renal function and of the skull are recommended.

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.

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/m² 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 \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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics (6 to 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 [14 CLINICAL TRIALS](#)). The pharmacokinetics of olmesartan medoxomil were evaluated in pediatric patients 6 to 16 years of age (see [10 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 APO-OLMESARTAN on blood pressure in neonates and pediatric patients with malignant hypertension.

Children < 1 year of age must not receive APO-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 to 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.

7.1.4 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 [14 CLINICAL TRIALS](#)).

8 ADVERSE REACTIONS

8.1 Adverse 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 / olmesartan medoxomil and hydrochlorothiazide in controlled trials: syncope, hypotension.

8.2 Clinical Trial Adverse 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 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) MedDRA Preferred term	Placebo N=555		Total Olmesartan Medoxomil N=2540	
	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)
Rhinitis	9	(1.6)	40	(1.6)
Pharyngitis	6	(1.1)	33	(1.3)
Sinusitis	11	(2)	29	(1.1)
Injury, poisoning and procedural complications				
Injury	7	(1.3)	34	(1.3)
Metabolism and nutrition disorders				
Hyperglycemia	15	(2.7)	32	(1.3)
Hypertriglyceridemia	6	(1.1)	29	(1.1)
Musculoskeletal and connective tissue disorders				

System Organ Class (SOC) MedDRA Preferred term	Placebo N=555		Total Olmesartan Medoxomil N=2540	
	N	%	N	%
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)
Renal and urinary disorders				
Hematuria	10	(1.8)	49	(1.9)

^aBody 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.

8.3 Less Common Clinical Trial Adverse 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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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> <u>(n=555)</u>	<u>Total Olmesartan Medoxomil</u> <u>(n=2450)</u>
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%)

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Pediatrics (6 to 16 years of age): No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified. The majority of treatment-emergent adverse events were mild or moderate in intensity and considered unrelated to study medication. Headache and dizziness were the most common AEs in children aged 6 to 16 years. There were no deaths.

8.6 Post-Market Adverse 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 Randomized 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 to 17.06)). The patient population at increased risk had preexisting coronary artery disease.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Not applicable

9.2 Overview

Not applicable

9.3 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Common name	Source of Evidence	Effect	Clinical comment
Agents Increasing Serum Potassium	T	APO-OLMESARTAN decreases the production of aldosterone,	Frequent monitoring of serum potassium is recommended. Potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia. Potassium-containing salt substitutes should be also used with caution.
Antacids	CT	The bioavailability of olmesartan was not significantly altered when co-administered with antacids [Al(OH) ₃ /Mg(OH) ₂].	
Cytochrome P450 Enzyme System	T	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	
Digoxin	CT	No pharmacokinetics or pharmacodynamics effects were reported when APO-OLMESARTAN was co-administered with digoxin in healthy volunteers.	
Diuretics	CT	Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally	The possibility of symptomatic hypotension with the use of APO-OLMESARTAN can be

Common name	Source of Evidence	Effect	Clinical comment
		<p>experience an excessive reduction in blood pressure after initiation of therapy with APO-OLMESARTAN No drug interaction of clinical significance has been identified with thiazide diuretics.</p>	<p>minimized by discontinuing the diuretic prior to initiation of treatment (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension in Volume- or Salt-Depleted Patients).</p>
<p>Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs</p>	<p>T</p>	<p>The use of Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs 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 m²).</p>	<p>Dual Blockade of the Renin-Angiotensin-System with ARBs, angiotensin converting enzyme (ACE) inhibitors 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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).</p>

Common name	Source of Evidence	Effect	Clinical comment
Lithium salts	T	As with other drugs which eliminate sodium, lithium clearance may be reduced in the presence of olmesartan.	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)	T	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. The antihypertensive effect of angiotensin II receptor antagonists, including olmesartan may be attenuated by NSAIDs including selective COX-2 inhibitors.	Renal function should be monitored periodically in patients receiving olmesartan and NSAID therapy.
Pravastatin	CT	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.

Common name	Source of Evidence	Effect	Clinical comment
Warfarin	CT	There was no effect on either the pharmacokinetics or pharmacodynamics of warfarin when co-administered with Olmesartan medoxomil in healthy volunteers.	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.4 Drug-Food Interactions

APO-OLMESARTAN may be administered with or without food.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

Not applicable

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT₁ 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 AT₁ receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT₂ receptor is found also in many tissues, but this receptor is not known to be

associated with cardiovascular homeostasis. Olmesartan has more than a 12,500 times greater affinity for the AT₁ receptor than for the AT₂ receptor.

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

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

10.2 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.

10.3 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: Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan.

Elimination: 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 to 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 CLR. However, the clinical relevance is unknown.

Sex: minor differences were observed in the pharmacokinetics of olmesartan in women compared to men. AUC and C_{max} were 10 to 15% higher in women than in men.

Ethnic origin: the antihypertensive effect of olmesartan was smaller in Black adult and pediatric (6 to 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.

11 STORAGE, STABILITY AND DISPOSAL

The tablets should be stored at room temperature between 15°C to 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

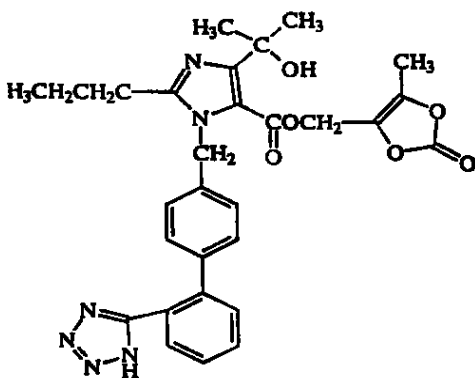
13 PHARMACEUTICAL INFORMATION

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: C₂₉H₃₀N₆O₆ and 558.59 g / mol

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).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Adults:

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.

14.2 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 angiotensin II receptor antagonist that binds selectively and competitively to the AT₁ receptor, with negligible binding to the AT₂ receptor. Olmesartan was shown to be both a potent and long-lasting angiotensin II 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 angiotensin II pressor response in rats is independent of cytochrome P450 metabolism.

14.3 Comparative Bioavailability Studies

Summary of studies establishing bioequivalence of APO-OLMESARTAN (Olmesartan Medoxomil) 40 mg Tablets to ^{Pr}Olmetec[®] (olmesartan medoxomil) 40 mg Tablets

A double blind, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study of 1 x 40 mg APO-OLMESARTAN (Olmesartan Medoxomil) tablets (Apotex Inc.) and 1 x 40 mg ^{Pr}Olmetec[®] (Olmesartan Medoxomil) tablets (Merck Canada Inc.) was conducted in 33 healthy, adult, male subjects under fasting conditions.

Olmesartan (1 x 40 mg Olmesartan Medoxomil Tablets) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference [†]	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng.h/mL)	11640.7 12135.8 (28.8)	11089.4 11689.5 (32.2)	105.0	96.4 - 114.3
AUC _I (ng.h/mL)	11815.2 12332.7 (29.4)	11244.0 11855.5 (32.3)	105.1	96.5 - 114.4
C _{max} (ng/mL)	1691.7 1760.6 (27.5)	1517.3 1608.7 (33.4)	111.5	101.8 - 122.1
T _{max} [§] (h)	2.0 (1.3 - 3.0)	2.0 (1.0 - 3.5)		
T _½ [€] (h)	8.5(14.6)	8.3 (14.3)		

*APO-OLMESARTAN (Olmesartan Medoxomil) 40 mg tablets Apotex Inc.

[†] ^{Pr}Olmetec[®] (Olmesartan Medoxomil) 40 mg tablets manufactured by Merck Canada Inc. Canada were purchased in Canada.

[§] Expressed as the median (range) only.

[€] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL 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/m² 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.

17 SUPPORTING PRODUCT MONOGRAPHS

- a. PrOlmetec® (20 mg and 40 mg, Olmesartan Medoxomil tablets), Submission Control number 250401, Product Monograph, Organon Canada Inc. (April 28, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr APO-OLMESARTAN

Olmesartan Medoxomil Tablets

Read this carefully before you start taking **APO-OLMESARTAN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-OLMESARTAN**.

Serious Warnings and Precautions

APO-OLMESARTAN should not be used during pregnancy. Taking APO-OLMESARTAN during pregnancy can cause harm and even death to your baby. If you discover that you are pregnant while taking APO-OLMESARTAN, stop the medication as soon as possible and contact your doctor.

What is APO-OLMESARTAN used for?

APO-OLMESARTAN is an angiotensin receptor blocker (ARB) 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.

How does APO-OLMESARTAN work?

APO-OLMESARTAN contains olmesartan medoxomil which is a drug that prevents the hormone, in your body that causes the blood vessels to constrict. APO-OLMESARTAN lowers blood pressure by relaxing your blood vessels.

APO-OLMESARTAN does not cure your high blood pressure. It helps to control it. Therefore, it is important to continue taking APO-OLMESARTAN regularly even if you feel fine.

What are the ingredients in APO-OLMESARTAN?

Medicinal ingredients: olmesartan medoxomil

Non-medicinal ingredients:

hydroxypropyl cellulose, hypromellose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, purified talc, and titanium dioxide.

APO-OLMESARTAN comes in the following dosage forms:

APO-OLMESARTAN film-coated tablets: 20 mg (white to off white, round, biconvex) or 40 mg (white to off white, oval, biconvex)

Do not use APO-OLMESARTAN if you:

- are allergic to olmesartan medoxomil or to any of the other ingredients of APO-OLMESARTAN
- have experienced an allergic reaction with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ARB. (You can recognize an ARB because its medicinal ingredient ends in “-SARTAN”) 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 APO-OLMESARTAN during pregnancy can cause harm and even death to your baby.
- are breastfeeding. It is possible that APO-OLMESARTAN passes into breast milk.
- have diabetes or kidney disease and are already taking a medicine that contains aliskiren (such as Rasilez) used to lower high blood pressure.

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-OLMESARTAN. Talk about any health conditions or problems you may have, including if you:

- have experienced an allergic reaction to any drug used to lower blood pressure.
- have a narrow heart valve or arteries.
- had a heart attack or have heart or blood vessel disease.
- had a stroke or have a condition that affects the blood supply to the brain.
- have liver or kidney disease.
- have blocked bile ducts.
- have diabetes.
- 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.
- are taking an angiotensin converting enzyme inhibitor (ACE Inhibitors). You can recognize ACE Inhibitors because their medicinal ingredient ends in “-PRIL”.
- are less than 18 years old or the drug is for your child.

Other warnings you should know about:

APO-OLMESARTAN can prevent the normal growth of your baby’s kidneys and skull if you take

the drug during the second and third trimester. Your doctor may recommend an ultrasound.

APO-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 APO-OLMESARTAN. Dizziness, lightheadedness, or fainting can occur when you take the drug for the first time and when your dosage is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with APO-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 converting enzyme inhibitors (ACE Inhibitors).
- Diuretics.
- 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).

How to take APO-OLMESARTAN

- APO-OLMESARTAN may be taken with or without food.
- Take exactly as directed by your doctor. Do NOT take more of it than prescribed.

Usual dose:

For adult patients:

- 20 mg tablet once daily.
- Can be increased to 40 mg once daily by your doctor if your blood pressure is not well controlled after two weeks of treatment.

For pediatric patients age (6 to 16 years old):

Weight between 20 kg to less than 35 kg:

- 10 mg once daily.
- Can be increased to 20 mg once daily by the doctor if blood pressure is not well controlled, after two weeks of treatment.

Weight of 35 kg or more:

- 20 mg once daily.
- Can be increased to 40 mg once daily if blood pressure is not well controlled after two weeks of treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-OLMESARTAN, contact a 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.

What are possible side effects from using APO-OLMESARTAN?

These are not all the possible side effects you may feel when taking APO-OLMESARTAN. If you experience any side effects not listed here, tell your healthcare professional.

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

Side effects may include:

- Back pain
- Decreased appetite
- Dizziness and headache
- Gastrointestinal problems
 - Constipation
 - Diarrhea
 - Nausea
 - Upset stomach
 - Vomiting
- Joint pain
- Muscle cramps, spasms and pain
- Rash, red itchy patches on skin
- Restlessness and weakness
- Upper respiratory infection
 - Congested and runny nose
 - Cough
 - Sore throat

APO-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	√		
Bronchitis: shortness of breath, weakness, high fever, coughing, fatigue, wheezing or whistling sound when breathing		√	
Hematuria (blood in urine): pink, red or very dark urine.		√	
UNCOMMON			
Ear Disorder (Vertigo): a sense of dizziness, spinning.		√	
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart.	√		
Hyperuricaemia (Increased levels of uric acid in the blood): swelling and redness in the joints.	√		
Chest Pain: Pressure or tightness in your chest	√		
Edema: unusual swelling of the arms, hands, legs, feet and ankles.	√		
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.		√	
RARE			
Acute Kidney Failure decrease or absence of urine, generalized swelling, weakness, shortness of breath, or irregular heartbeats, loss of appetite, lethargy and fatigue.			√
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.		√	
Increased Levels of Potassium in the Blood: irregular heartbeats, muscle weakness and generally feeling unwell.		√	

UNKNOWN			
Sprue-like Enteropathy: severe chronic diarrhea with substantial weight loss.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

<p>Reporting Side Effects</p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> • Visiting the Web page on Adverse Reaction Reporting (https://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. <p><i>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.</i></p>
--

Storage:

The tablets should be stored at room temperature between 15°C to 30°C.

Keep out of sight and reach of children and pets.

If you want more information about APO-OLMESARTAN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting 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 (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last Revised: August 3, 2022