

Product Monograph

Including Patient Medication Information

^{Pr}Auro-Azilsartan Medoxomil

Azilsartan Medoxomil (as azilsartan medoxomil potassium)

Tablets for oral use

40 mg and 80 mg

Angiotensin II AT1 Receptor Blocker

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Recent Major Label Changes

[7 Warnings and precautions, Gastrointestinal](#)

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1. Indications

- Auro-Azilsartan Medoxomil (azilsartan medoxomil) is an angiotensin II receptor blocker (ARB) indicated for the treatment of mild to moderate essential hypertension.
- Auro-Azilsartan Medoxomil may be used alone or concomitantly with thiazide diuretics or calcium channel blockers.

1.1. Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics (≥ 75 years)

No initial dose adjustment with Auro-Azilsartan Medoxomil is necessary in elderly patients. Abnormally high serum creatinine values were more likely to be reported for patients aged ≥75 years. No other differences in safety or efficacy were observed between elderly patients and younger patients, but caution should be exercised in patients aged ≥75 years who may be at risk for hypotension

2. Contraindications

Auro-Azilsartan Medoxomil (azilsartan medoxomil) is contraindicated in:

- Patients who are hypersensitive to azilsartan medoxomil or to any ingredient in the formulation or component of the container. For a complete listing, see the [6 Dosage Forms, Composition and Packaging](#) section of the product monograph.
- Combination with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m²) (see [7 Warnings and Precautions, Cardiovascular, Dual Blockade of the Renin-Angiotensin System \(RAS\)](#) and [Renal](#), and [9.4 Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin-System \(RAS\) with ARBs, ACEIs or aliskiren-containing drugs](#)).
- Pregnancy (see [7.1.1.Pregnancy](#)).
- Nursing women (see [7.1.2 Breast-Feeding](#)).

3. Serious Warnings and Precautions Box

When used in pregnancy, angiotensin receptor (AT1) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, Auro-Azilsartan Medoxomil (azilsartan medoxomil) should be discontinued as soon as possible (see [7.1 Special Populations](#)).

4. Dosage and Administration

4.1 Dosing Considerations

Geriatrics

No initial dose adjustment with Auro-Azilsartan Medoxomil is necessary in elderly patients. Abnormally high serum creatinine values were more likely to be reported for patients aged ≥ 75 years. No other differences in safety or efficacy were observed between elderly patients and younger patients, but caution should be exercised in patients aged ≥ 75 years who may be at risk for hypotension.

Hepatic Impairment

Azilsartan medoxomil has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group. As total exposure is increased in mild and moderate hepatic impairment patients, care should be exercised, and a lower starting dose is recommended in patients with liver diseases, and the maximum dose of 80 mg Auro-Azilsartan Medoxomil 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 azilsartan is eliminated in the bile.

Renal Impairment:

Caution should be exercised in patients with severe renal impairment and ESRD as there is no experience on the use of azilsartan medoxomil in these patients. No dose adjustment is required in patients with mild or moderate renal impairment.

Intravascular volume or salt depletion

Correct volume and/or salt depletion prior to administration.

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose in adults is 40 mg taken orally once daily. The dose may be increased to a maximum of 80 mg once daily when additional blood pressure reduction is required.

Auro-Azilsartan Medoxomil may be taken with or without food.

4.5 Missed Dose

If a dose of Auro-Azilsartan Medoxomil is missed at its usual time, it should be taken as soon as possible. However, if it is too close to the time of the next dose, the missed dose should be skipped, and treatment should be resumed with the next scheduled dose. A double dose should not be taken.

5. Overdose

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.

Hemodialysis does not remove azilsartan from the systemic circulation.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|-------------------------|------------------------------------|---|
| Oral | Tablet 40 mg, 80 mg | Croscarmellose sodium, HPMC 2910 / Hypromellose, hydroxy propyl cellulose, iron oxide yellow, macrogol/PEG, magnesium aluminosilicate, magnesium stearate, mannitol, microcrystalline cellulose, talc and titanium dioxide. |

Description

Auro-Azilsartan Medoxomil is supplied in the following dosage strengths:

- 40 mg tablets: White to Off-white, round film coated tablets, debossed with 'AL' on one side and '40' on the other side.
- 80 mg tablets: White to Off-white, round film coated tablets, debossed with 'AL' on one side and '80' on the other side.

Packaging: HDPE bottles of 30 and 100 tablets and Blister pack of 3x10's count

7. Warnings and Precautions

(See [3 Serious Warnings and Precautions Box.](#))

Cardiovascular

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin-aldosterone-system (RAAS), 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 azilsartan medoxomil. The condition should be corrected prior to administration of Auro-Azilsartan Medoxomil, or treatment should be started under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

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.

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.

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin receptor blockers (ARBs), such as azilsartan medoxomil, or of angiotensin converting enzyme inhibitors (ACEIs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m²). Therefore, the use of Auro-Azilsartan Medoxomil in combination with aliskiren-containing drugs is contraindicated in these patients (see [2 Contraindications](#)).

Further, co-administration of ARBs, including Auro-Azilsartan Medoxomil, with other agents blocking the RAS, such as ACEIs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Gastrointestinal

Intestinal angioedema: Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including azilsartan. These patients presented with abdominal pain (with or without nausea, vomiting or diarrhoea). Symptoms resolved after discontinuation of angiotensin II receptor antagonists. Intestinal angioedema should be included in the differential diagnosis of patients treated with angiotensin II receptor antagonists presenting with abdominal pain. If intestinal angioedema is diagnosed, Auro-Azilsartan Medoxomil should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Hepatic/Biliary/Pancreatic

Azilsartan medoxomil has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patients group. As total exposure is increased in mild and moderate hepatic impaired patients, care should be exercised, and a lower starting dose is recommended in patients with liver diseases, and the maximum dose of 80 mg Auro-Azilsartan Medoxomil 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 azilsartan is eliminated in the bile (see [10 Clinical Pharmacology](#)).

Immune

Angioedema

One case of angioedema was reported and possibly related to the use of azilsartan medoxomil. Angioedema has been reported with other ARBs. There is a potential risk of angioedema with the use of azilsartan medoxomil. If angioedema of the face, extremities, lips, tongue, or glottis occurs, Auro-Azilsartan Medoxomil should be discontinued immediately, the patient should be treated appropriately

in accordance with accepted medical care, and carefully observed until the symptoms and signs disappear.

Patients with a known hypersensitivity (anaphylaxis) or angioedema to ARBs should not be treated with Auro-Azilsartan Medoxomil.

Musculoskeletal

Cases of myopathy/rhabdomyolysis have been reported in patients treated with azilsartan medoxomil. In patients who develop unexplained myalgia and muscle weakness, elevated blood creatine phosphokinase, and elevated blood/urine myoglobin, administration should be discontinued, and appropriate measures taken. Caution should be exercised in the development of acute renal failure due to rhabdomyolysis.

Renal

As a consequence of inhibiting the RAAS, changes in renal function may be anticipated in susceptible individuals treated with azilsartan medoxomil. In patients whose renal function may depend on the activity of the RAAS (e.g., patients with severe congestive heart failure, renal artery stenosis, or volume depletion), treatment with ACEIs and ARBs has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Similar results may be anticipated in patients treated with azilsartan medoxomil (see [10 Clinical Pharmacology](#)).

The use of ARBs – including azilsartan medoxomil – or ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m²) (see [2 Contraindications](#) and [9.4 Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin-System \(RAS\) with ARBs, ACEIs, or aliskiren-containing drugs](#)).

In studies of ACEIs 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 azilsartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected with the use of azilsartan medoxomil.

Use of Auro-Azilsartan Medoxomil should include appropriate assessment of renal function. Caution should be exercised in hypertensive patients with severe renal impairment and end-stage renal disease (ESRD) as there is no experience on the use of azilsartan medoxomil in these patients. No dose adjustment is required in patients with mild or moderate renal impairment (see [10 Clinical Pharmacology](#)).

There is currently no experience on the use of azilsartan medoxomil in patients who have recently undergone kidney transplantation.

7.1. Special Populations

7.1.1 Pregnancy

Drugs that act directly on RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, Auro-Azilsartan Medoxomil should be discontinued as soon as possible.

The use of ARBs is contraindicated during pregnancy (see [2 Contraindications](#)). Epidemiological evidence regarding the risk of teratogenicity following exposure to ACEIs (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 ARBs, similar risks may exist for azilsartan medoxomil. 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 ARBs 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 histories 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, there is limited experience with these procedures, which have not been associated with significant clinical benefit.

Hemodialysis does not remove azilsartan from the systemic circulation.

Animal Data

Azilsartan medoxomil administered to pregnant rats from gestation day 6 to lactation day 21 at 10 mg/kg/day produced adverse effects on pup viability, delayed incisor eruption, and dilatation of the renal pelvis along with hydronephrosis. This oral dose was associated with a systemic exposure (AUC) to azilsartan in non-pregnant rats of about 4.5x that in humans given 80 mg/day. When administered from gestation days 6-17 or 18 embryo-fetal toxicity occurred at azilsartan medoxomil doses of 1,000 mg/kg/day in rats (dilated renal pelvis and short supernumerary ribs) and 50 mg/kg/day in rabbits (post-implantation loss, embryo-fetal deaths, and decreased number of live fetuses). The azilsartan systemic exposure at the no-observed-adverse-effect levels (NOAELs) (100 mg/kg/day in rats and 30 mg/kg/day in rabbits,) was estimated at 20x and 9x that achieved in humans given 80 mg/day, respectively.

7.1.2. Breastfeeding

It is not known whether azilsartan medoxomil is excreted in human milk, but it has been found 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 (see [2 Contraindications](#)).

7.1.3. Pediatrics

Safety and efficacy in pediatric patients have not been established. Therefore, Auro-Azilsartan Medoxomil is not indicated in this patient population.

7.1.4. Geriatrics

No initial dose adjustment with Auro-Azilsartan Medoxomil is necessary in elderly patients. Abnormally high serum creatinine values were more likely to be reported for patients aged ≥ 75 years. No other differences in safety or efficacy were observed between elderly patients and younger patients, but caution should be exercised in patients aged ≥ 75 years who may be at risk for hypotension.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Treatment with azilsartan medoxomil was generally well tolerated across clinical trials. The overall incidence of adverse reactions was comparable to placebo. In placebo-controlled monotherapy and combination therapy trials:

- **Withdrawal due to adverse events** occurred in:
 - 2.4% of patients receiving placebo (19/801)
 - 2.2% of patients receiving azilsartan medoxomil 40 mg (24/1072)
 - 2.7% of patients receiving azilsartan medoxomil 80 mg (29/1074)

The most commonly reported adverse reactions included:

- Diarrhea
- Dizziness
- Fatigue
- Increased serum creatinine

These reactions were typically mild to moderate in intensity and transient in nature. Serious adverse events were rare and occurred at rates similar to placebo.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Azilsartan medoxomil (was evaluated for safety in a total of 4814 patients in clinical trials. There were 1704 patients treated for ≥ 6 months and 588 for ≥ 1 year.

The rates of withdrawals due to adverse events (AEs) in placebo-controlled monotherapy and combination therapy trials were 2.4 % (19/801) for placebo, 2.2% (24/1072) for azilsartan medoxomil 40 mg, and 2.7% (29/1074) for azilsartan medoxomil 80 mg.

In the placebo-controlled monotherapy studies, treatment-emergent AEs occurring at an incidence of $\geq 1\%$ in patients treated with azilsartan medoxomil are presented in Table 1.

Table 2- Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Patients

| | Placebo (n=435) Case (%) | Azilsartan medoxomil 40 mg (n=698) Case (%) | Azilsartan medoxomil 80 mg (n=704) Case (%) |
|--|---|--|--|
| General | | | |
| Edema | 6 (1.4%) | 13 (1.9%) | 14 (2.0%) |
| Fatigue | 2 (0.5%) | 6 (0.9%) | 14 (2.0%) |
| Cardiovascular | | | |
| Arrhythmia | 1 (0.2%) | 8 (1.2%) | 4 (0.6%) |
| Ear/Nose /Throat | | | |
| Nasopharyngitis | 6 (1.4%) | 10 (1.4%) | 17 (2.4%) |
| Endocrine and Metabolism | | | |
| Dyslipidemia | 6 (1.4%) | 19 (2.7%) | 23 (3.3%) |
| Hypertriglyceridemia | 4 (0.9%) | 8 (1.1%) | 8 (1.1%) |
| Gastrointestinal | | | |
| Diarrhea | 2 (0.5%) | 11 (1.6%) | 17 (2.4%) |
| Nausea | 2 (0.5%) | 7 (1.0%) | 8 (1.1%) |
| Genitourinary | | | |
| Urinary tract infection | 13 (3.0%) | 17 (2.4%) | 17 (2.4%) |
| Musculoskeletal and Connective Tissue | | | |
| Arthralgia | 3 (0.7%) | 5 (0.7%) | 8 (1.1%) |
| Back pain | 4 (0.9%) | 4 (0.6%) | 8 (1.1%) |
| Myalgia | 1 (0.2%) | 2 (0.3%) | 8 (1.1%) |
| Pain in extremity | 5 (1.1%) | 2 (0.3%) | 7 (1.0%) |
| Neurology | | | |
| Headache | 27 (6.2%) | 33 (4.7%) | 37 (5.3%) |
| Dizziness | 9 (2.1%) | 20 (2.9%) | 21 (3.0%) |
| Respiratory | | | |
| Upper respiratory tract infection | 6 (1.4%) | 3 (0.4%) | 13 (1.8%) |
| Monitoring and Laboratory Tests | | | |
| Blood creatine phosphokinase (CPK) increased | 8 (1.8%) | 14 (2.0%) | 11 (1.6%) |
| C-reactive protein (CRP) increased | 4 (0.9%) | 5 (0.7%) | 9 (1.3%) |
| Plasminogen activator inhibitor increased | 7 (1.6%) | 12 (1.7%) | 13 (1.8%) |

8.3 Less Common Clinical Trial Adverse Reactions

The following AEs were reported at an incidence of <1% in placebo-controlled clinical trials (in >1 patient, with higher frequency than placebo):

- **Blood and Lymphatic System Disorder:** Anemia, Leukopenia
- **Ear and Labyrinth Disorders:** Vertigo
- **Gastrointestinal Disorders:** Abdominal discomfort, Abdominal pain, Constipation, Diarrhea, Dry mouth, Dyspepsia, Nausea, Toothache, Vomiting,
- **General Disorders and Administration Site Conditions:** Fatigue, Feeling abnormal, Oedema peripheral
- **Metabolism and Nutrition Disorders:** Dyslipidemia, Hyperkalemia, Hypertriglyceridemia
- **Musculoskeletal and Connective Tissue Disorders:** Muscle spasms, Musculoskeletal pain, Myalgia, Pain in extremity, Rhabdomyolysis
- **Nervous System Disorders:** Dizziness, Headache, Sinus headache
- **Psychiatric Disorders:** Anxiety
- **Renal and Urinary Disorders:** Pollakiuria, Proteinuria
- **Reproductive System and Breast Disorders:** Erectile dysfunction
- **Respiratory, Thoracic and Mediastinal Disorders:** Cough, Oropharyngeal pain, Sinus congestion
- **Skin and subcutaneous Tissue Disorders:** Angioedema, Dermatitis, Hyperhidrosis, Pruritis, Urticaria
- **Vascular Disorders:** Hypertension, Hypotension

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

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommon with administration of azilsartan medoxomil .

- **Blood creatine phosphokinase:** High levels of creatine phosphokinase were observed in 0.3% of patients treated with azilsartan medoxomil. and 0.3% of patients treated with placebo.
- **Serum creatinine:** Small reversible increases in serum creatinine were seen in patients receiving azilsartan medoxomil. The increase may be larger when coadministered with chlorthalidone or hydrochlorothiazide. In addition, patients taking azilsartan medoxomil who had moderate to severe

renal impairment at baseline or who were >75 years of age were more likely to report with serum creatinine increases.

Increases in low density lipoprotein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood uric acid were seen in <1% of patients treated with azilsartan medoxomil.

- **Hemoglobin and Hematocrit:** Low hemoglobin, hematocrit, and red blood cell (RBC) counts were observed in 0.2%, 0.4%, and 0.3% of azilsartan medoxomil -treated subjects, respectively. None of these abnormalities were reported in the placebo group. Markedly abnormal (low or high) platelet and white blood cell (WBC) counts were observed in <0.3% of subjects.

8.5. Post-Market Adverse Reactions

The following adverse reactions have been identified during the post-approval use of azilsartan medoxomil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Gastrointestinal Disorders:** Nausea, Intestinal angioedema
- **Musculoskeletal and Connective Tissue Disorders:** Arthralgia, muscle spasms, rhabdomyolysis
- **Skin and subcutaneous Tissue Disorders:** Angioedema, Pruritus, Rash

9. Drug Interactions

9.4. Drug-Drug Interactions

Table 3- Established or Potential Drug-Drug Interaction

| Common Name | Source of Evidence | Effect | Clinical comment |
|-----------------------------------|--------------------|--|---|
| Agents increasing serum potassium | C | Azilsartan reduces 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. Concomitant thiazide diuretic use may attenuate any effect that azilsartan may have on serum potassium. |
| Amlodipine | CT | Concomitant administration of azilsartan medoxomil and amlodipine has no effect on steady state pharmacokinetics of amlodipine or azilsartan, but there is isolated transient systolic blood pressure reduction. | There is a possibility of symptomatic hypotension with the concomitant use of azilsartan medoxomil and amlodipine. |

| Common Name | Source of Evidence | Effect | Clinical comment |
|--|--------------------|---|---|
| Antacid | CT | In a short-term study, concomitant administration azilsartan medoxomil and antacid liquid results in a small (18%) decrease in AUC(0-inf) of azilsartan and T _{max} delay for 1.5 hour. There is no change in azilsartan C _{max} . | - |
| Caffeine, Midazolam, tolbutamide, Dextromethorphan, Fexofenadine cocktail | CT | Azilsartan administered as 40 mg for 5 days, has no clinically significant effect (inhibition or induction) on CYP1A2, CYP2C9, CYP2D6, CYP3A4 or PgP activity. | - |
| | CT | Azilsartan medoxomil administered as 80 mg for 5 days has no clinically significant effect (inhibition or induction) on CYP1A2, CYP2C9, CYP2D6 or CYP3A4. Fexofenadine AUC and C _{max} were reduced by over 25%, but T _{max} was not changed. | PgP may be affected by the use of azilsartan medoxomil, but the clinical impact is unknown. |
| Digoxin | CT | No significant PK changes are found following coadministration of azilsartan medoxomil and digoxin, which is a PgP substrate. | - |
| Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren containing drugs | CT | Dual Blockade of the Renin-Angiotensin-System with ARBs, ACEIs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or moderate to severe renal impairment (GFR <60 ml/min/1.73m ²), and is generally not recommended in 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, Cardiovascular, Dual Blockade of the Renin-Angiotensin-System (RAS) . |
| Fluconazole | CT | Concomitant administration of azilsartan and fluconazole (a potent CYP2C9/CYP2C19 inhibitor) increases azilsartan plasma AUC(0-inf) by 42%, C _{max} by 14%, and urinary exposure XU (0-24) by 48%. There are no significant effects on azilsartan T _{1/2} (13.0 hr vs 12.2 hr) or T _{max} values (1.73 hr vs 1.76 hr). | CYP2C9/CYP2C19 may be involved in azilsartan medoxomil metabolism, but the clinical impact is unknown. |
| Glyburide | CT | Concomitant administration of azilsartan and glyburide has no effect in glyburide AUC and C _{max} . Glyburide T _{max} is earlier by 30 minutes. | - |
| Ketoconazole | CT | Concomitant administration of azilsartan and ketoconazole (a potent CYP3A4 inhibitor) reduces azilsartan plasma AUC(0-inf) by 21% and C _{max} by 32%. T _{max} values are delayed by 1 hour (3.21 vs 2.06 hr). | CYP3A4 may be involved in azilsartan medoxomil metabolism but the clinical impact is unknown. |
| Lithium salts | T | Lithium clearance may be reduced. | Serum lithium levels should be monitored carefully if lithium salts are to be administered. |

| Common Name | Source of Evidence | Effect | Clinical comment |
|--|--------------------|--|---|
| Metformin | CT | Concomitant administration of azilsartan and metformin has no change in azilsartan AUC or C _{max} . Azilsartan T _{max} is delayed by 30 minutes. Concomitant administration results in a 20% decrease in metformin AUC and a 18% decrease in metformin C _{max} . There is no change in metformin T _{max} . | - |
| NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) | 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 ARBs, including azilsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ARBs, including azilsartan may be attenuated by NSAIDs including selective COX-2 inhibitors. | Renal function should be monitored periodically in patients receiving azilsartan and NSAID therapy, including selective COX-2 inhibitors. |
| Pioglitazone | CT | Concomitant administration has no effect on azilsartan or pioglitazone AUC or T _{max} . There is a 14% increase in pioglitazone C _{max} ; there is no change in azilsartan C _{max} . | - |
| Warfarin | CT | Concomitant administration had no effect on warfarin AUC or C _{max} . No change is found in pharmacodynamics (PT or INR). S-warfarin T _{max} was earlier by 15 minutes; there was no change in S-warfarin T _{max} . | - |

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

9.5. Drug-Food Interactions

Auro-Azilsartan Medoxomil may be taken with or without food.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Azilsartan medoxomil, a prodrug, is hydrolyzed to azilsartan during absorption from the gastrointestinal tract. Azilsartan is a selective AT1 subtype angiotensin II receptor blocker (ARB).

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzymes (ACE, kinase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS), with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Azilsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathway for angiotensin II synthesis.

An AT2 receptor is also found in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Azilsartan has >10,000-fold greater affinity for the AT1 receptor than for the AT2 receptor.

Because azilsartan does not inhibit ACE (kinase II), it should 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 angiotensin II circulating level do not overcome the effect of azilsartan on blood pressure.

10.2 Pharmacodynamics

Azilsartan inhibits the pressor effects of an angiotensin II infusion in a dose-related manner. An azilsartan single dose equivalent to 32 mg azilsartan medoxomil inhibited the maximal pressor effect by approximately 90% at peak, and approximately 60% at 24 hours. In healthy subjects, single and repeated administrations of azilsartan medoxomil increased plasma angiotensin I and II concentrations and plasma renin activity while decreasing plasma aldosterone concentrations; no clinically significant effects on serum potassium or sodium were observed.

In Black patients, who tend to have low-renin hypertension, less blood pressure reduction was observed with azilsartan medoxomil compared with non-Black patients.

Effect on Cardiac Electrocardiography: A randomized, double-blind, placebo- and positive-controlled crossover study was performed to assess the potential of azilsartan to prolong the QTc interval in healthy subjects (N=58). Azilsartan medoxomil was administered as a single 320 mg dose. No clinically or statistically significant effects on the QTc interval were observed.

10.3 Pharmacodynamics

Table 3 – Summary of pharmacokinetic parameter estimates (arithmetic mean ± S.D.) for azilsartan after single and multiple oral doses of azilsartan medoxomil in healthy subjects

| | N | C _{max} (ng/mL) | T _{1/2} (h) | AUC (ng·hr/mL) |
|--|----|-----------------------------|-------------------------|--------------------|
| Azilsartan medoxomil 40 mg, Single Dose | 47 | 2,549 ± 824 | 11.70 ± 2.83 | 21,036 ± 7,061 |
| Azilsartan medoxomil 80 mg, Single Dose | 74 | 5,170 ± 1,491 | 11.38 ± 2.03 | 40,010 ± 11,043 |

| | | | | |
|---|----|------------------|----|--------------------|
| Azilsartan medoxomil 40 mg, Multiple Doses to Steady-State | 23 | 2,554 ± 652 | ND | 18,156 ± 5,146 |
| Azilsartan medoxomil 80 mg, Multiple Doses to Steady-State | 53 | 5,626 ± 1,273 | ND | 42,488 ± 11,169 |

N: Number of Subjects.

C_{max} : peak plasma concentration

$T_{1/2}$: elimination half-life.

AUC: area under plasma concentration curve

AUC_{0-inf} is presented for single dose and

AUC_{0-tau} is presented for multiple dose

ND: Not determined.

Absorption

Azilsartan medoxomil is rapidly hydrolyzed to azilsartan, a selective antagonist of angiotensin AT1 receptors, in the gastrointestinal tract during absorption. Dose proportionality in exposure was established for azilsartan in the azilsartan medoxomil dose range of 20-320 mg after single or multiple dosing.

The estimated absolute bioavailability of azilsartan medoxomil based on levels of azilsartan is approximately 60%. After oral administration of azilsartan medoxomil, peak plasma concentrations (C_{max}) of azilsartan are reached within 1.5-3 hours. Food does not affect the bioavailability of azilsartan.

Distribution

The volume of distribution of azilsartan is approximately 16L. Azilsartan is highly bound to human plasma proteins (>99%), mainly serum albumin. Protein binding is constant at azilsartan plasma concentrations well above the range achieved with recommended doses. In rats, minimal azilsartan-associated radioactivity crossed the blood-brain barrier. Azilsartan and all related metabolites passed across the placental barrier in pregnant rats and were distributed to the fetus.

Metabolism

Azilsartan is metabolized to two primary metabolites. The major metabolite in plasma is formed by O-dealkylation, referred to as metabolite M-II, and the minor metabolite is formed by decarboxylation, referred to as metabolite M-I. Systemic exposures to the major and minor metabolites in humans were approximately 50% and <1% of azilsartan, respectively. M-I and M-II do not contribute to the pharmacologic activity of azilsartan medoxomil. The major enzyme responsible for azilsartan metabolism is CYP2C9.

Elimination

Following an oral dose of 14C-labeled azilsartan medoxomil, approximately 55% of radioactivity was recovered in feces and approximately 42% in urine, with 15% of the dose excreted in urine as azilsartan. The elimination half-life of azilsartan is approximately 11 hours and renal clearance is approximately 2.3 mL/min. Steady-state levels of azilsartan are achieved within 5 days and no accumulation in plasma occurs with repeated once-daily dosing.

Special Populations and Conditions

The effect of demographic and functional factors on the pharmacokinetics of azilsartan was studied in single and multiple dose studies. Effects are modest and do not call for dosage adjustment.

- **Pediatrics:** Pharmacokinetics of azilsartan has not been studied in patients <18 years of age.
- **Geriatrics:** Pharmacokinetics of azilsartan do not differ significantly between young (age range 18-45) and elderly (age range 65-85) subjects.
- **Sex:** Pharmacokinetics of azilsartan do not differ significantly between males and females. No dose adjustment is necessary based on gender.
- **Ethnic Origin:** Pharmacokinetics of azilsartan do not differ significantly between the black and white populations.
- **Hepatic Insufficiency:** Azilsartan medoxomil has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patients group. Total exposure (AUC) was increased by 64% in moderate and by 28% in mild hepatic impairment patients.
- **Renal Insufficiency:** Total exposure to azilsartan, after a single dose of azilsartan medoxomil, increases by 30%, 25%, and 96%, in subjects with mild, moderate, and severe renal impairment, respectively. Hemodialysis does not remove azilsartan from the systemic circulation.

11. Storage, Stability and Disposal

Store at 15-30°C. Keep container tightly closed. Protect from moisture and light.

12. Special Handling Instructions

Do not repackage Auro-Azilsartan Medoxomil.

Dispense and store Auro-Azilsartan Medoxomil in its original container with provided desiccant to protect Auro-Azilsartan Medoxomil from light and moisture

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Proper name: Azilsartan Medoxomil

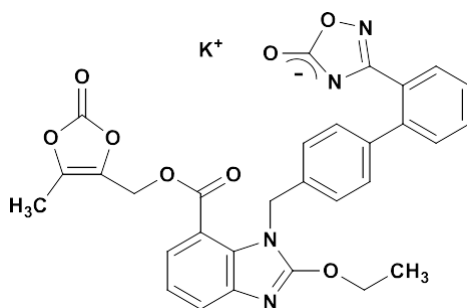
Chemical name: (5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl 2-ethoxy-1- {[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl] methyl} -1H-benzimidazole-7-carboxylate monopotassium salt.

Molecular formula: $C_{30}H_{23}KN_4O_8$

Molecular mass: Azilsartan medoxomil potassium: 606.62 g/mol

Azilsartan medoxomil: 568.53 g/mol

Structural formula:



Physicochemical properties

Solubility: Azilsartan medoxomil potassium is practically insoluble in water and freely soluble in methanol.

14. Clinical Trials

14.1. Trial Design and Study Demographics

Table 4 - Summary of patient demographics for clinical trials

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---------|--|--|--------------------|------------------------|----------------|
| Study 1 | Double-blind, randomized, placebo-controlled | Azilsartan medoxomil 20 mg titrated to 40 mg | N=280 | 56 years (22-84 years) | 54% M 46% F |
| | | Azilsartan medoxomil 40 mg titrated to 80 mg | N=285 | | |
| | | Placebo | N=154 | | |
| Study 2 | Double-blind, randomized, placebo-controlled | Azilsartan medoxomil 20 mg | N=283 | 58 years (21-86 years) | 50% M 50% F |
| | | Azilsartan medoxomil 40 mg | N=283 | | |
| | | Azilsartan medoxomil 80 mg | N=285 | | |
| | | Placebo | N=142 | | |
| | | Oral administration 2 weeks titration and 4 weeks treatment | | | |
| | | Oral administration 6 weeks | | | |

14.2 Study Results

Two 6-week randomized, double blind studies (Study 1 and Study 2) compared the efficacy on blood pressure of azilsartan medoxomil at doses of 40 mg and 80 mg, with placebo. Blood pressure reductions compared to placebo based on clinic blood pressure measurements at trough and 24 hours mean blood pressure by ambulatory blood pressure monitoring (ABPM) are shown in Table 5 for both studies. Azilsartan medoxomil was statistically superior to placebo for both clinic and 24 hours mean blood pressure measurements.

Table 5 - Placebo-Corrected Mean Change from Baseline in Systolic / Diastolic Blood Pressure at 6 Weeks (mm Hg)

| | Study 1 | | Study 2 | |
|----------------------------|---|--|---|--|
| | Clinic Blood Pressure (Mean Baseline 157.4 / 92.5) | 24 Hour Mean by ABPM (Mean Baseline 144.9 / 88.7) | Clinic Blood Pressure (Mean Baseline 159.0 / 91.8) | 24 Hour Mean by ABPM (Mean Baseline 146.2 / 87.6) |
| Azilsartan medoxomil 40 mg | -14.6 / -6.2 | -13.2 / -8.6 | -12.4 / -7.1 | -12.1 / -7.7 |
| Azilsartan medoxomil 80 mg | -14.9 / -7.5 | -14.3 / -9.4 | -15.5 / -8.6 | -13.2 / -7.9 |

Note – All active treatments lead to significantly greater reduction SBP and DBP vs placebo.

Maximum dose achieved in study 1. Azilsartan medoxomil doses were force-titrated at Week 2 from 20 to 40 mg and from 40 to 80 mg.

Figure 1 shows the 24-hour ambulatory systolic and diastolic blood pressure profiles at endpoint for study 1.

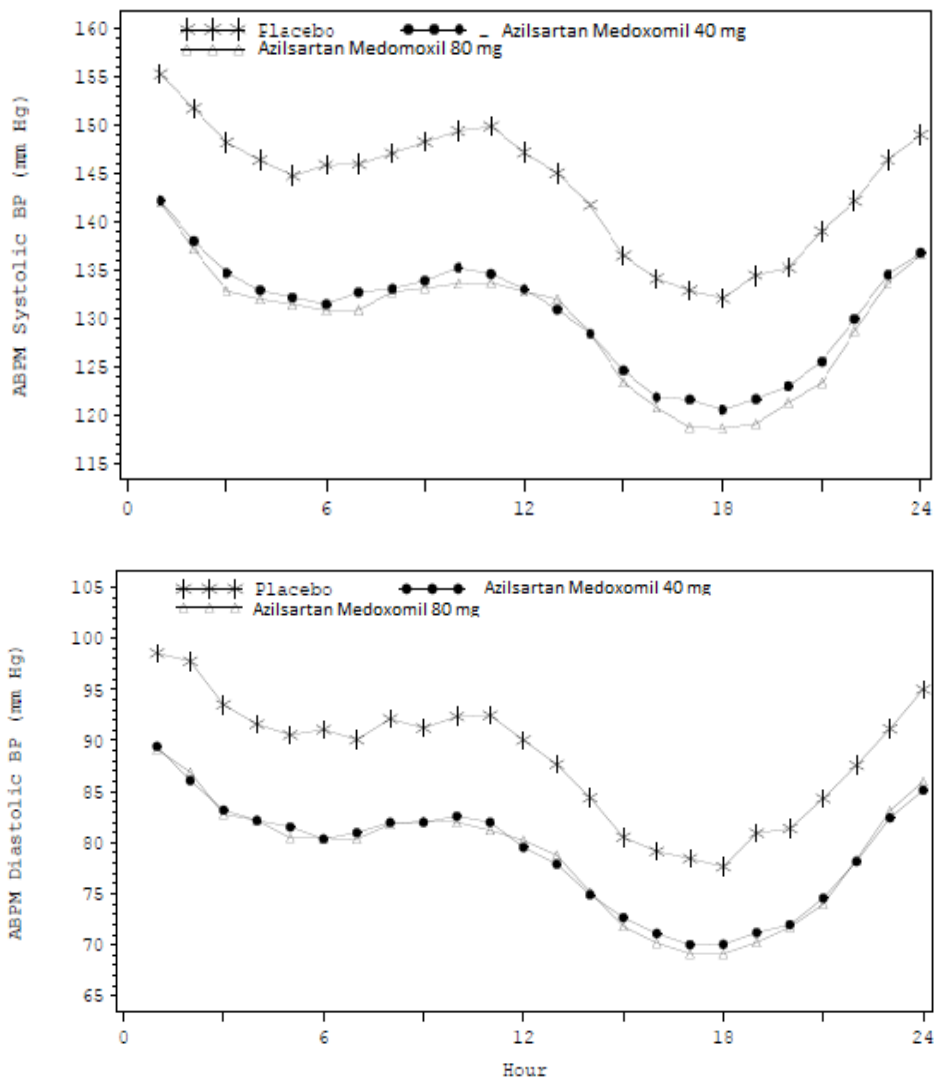


Figure 1: Mean Ambulatory Systolic/Diastolic Blood Pressure at 6 weeks by Dose and Hour

Most of the antihypertensive effect occurs within the first 2 weeks of dosing.

Azilsartan medoxomil was effective in reducing blood pressure regardless of the age, gender, or race of patients, but the effect, as monotherapy, was smaller, approximately half, in black patients, who tend to have low renin levels, as has been seen with ACE inhibitors and other ARBs.

Azilsartan medoxomil 40 and 80 mg co-administered with a calcium channel blocker (amlodipine), or a thiazide-type diuretic (chlorthalidone) resulted in additional blood pressure reductions.

In a controlled trial, when azilsartan medoxomil 40 mg or 80 mg was added on to Chlorthalidone (25 mg) treatment, the resulting decrease in blood pressure was larger than that observed with Chlorthalidone alone.

In a controlled trial, when azilsartan medoxomil 40 mg or 80 mg was added on to Amlodipine (5 mg) treatment, the resulting decrease in blood pressure was larger than that observed with Amlodipine alone.

14.3 Comparative Bioavailability Studies

A double blind, randomized, two-treatment, two-sequence, two-period crossover single dose (1 x 80 mg) oral bioequivalence study of Auro-Azilsartan (Auro Pharma Inc. (Canada)) *versus* EDARBI® (Valeant Canada LP Valeant Canada S.E.C.) was conducted in 42 healthy adult human male subjects under fasting conditions. A summary of the bioavailability data based on the metabolite, azilsartan, from 38 subjects who completed the study is presented in the following table.

Summary Table of the Comparative Bio-Availability Data

| Azilsartan (1 x 80 mg azilsartan medoxomil (as azilsartan medoxomil potassium)) From measured data Geometric Mean Arithmetic Mean (CV %) | | | | |
|--|---------------------------|---------------------------|----------------------------|-------------------------|
| Parameter | Test ¹ | Reference ² | % Ratio of Geometric Means | 90% Confidence Interval |
| AUC _T (ng•h/mL) | 32165.4 33118.6 (23.5) | 33473.7 34539.9 (22.5) | 96.1 | 89.7-102.9 |
| AUC _C ³ (ng•h/mL) | 33646.3 34551.1 (22.1) | 34815.8 35911.7 (22.8) | 96.6 | 90.6–103.1 |
| C _{max} (ng/mL) | 4146.9 4275.4 (26.7) | 4300.9 4368.0 (19.0) | 96.4 | 89.6-103.8 |
| T _{max} ⁴ (h) | 1.84 (1.00 – 4.00) | 2.00 (1.00 – 5.00) | | |
| T _½ ⁵ (h) | 9.77 (18.2) | 9.83 (24.2) | | |

¹Auro-Azilsartan (azilsartan medoximal (as asilsartan medoxomil potassium)) tablets, 80 mg (Auro Pharma Inc.).

² EDARBI® (azilsartan medoxomil as (azilsartan medoxomil potassium)) tablets, 80 mg (Valeant Canada LP Valeant Canada S.E.C.).

³ N=37.

⁴ Expressed as the median (range) only.

⁵ Expressed as arithmetic mean (% CV) only.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

Azilsartan medoxomil (pro-drug), azilsartan (active drug) and M-II (main metabolite in human) were evaluated in a program of toxicology studies including: acute and repeat-dose studies in rodents and dogs; genotoxicity studies; rodent carcinogenicity studies and reproductive and developmental studies in rats and rabbits. Essentially there was overlap and concordance of findings in the toxicology studies for azilsartan medoxomil and azilsartan; therefore, mainly findings in studies with azilsartan medoxomil are described in the following section.

The M-II metabolite had a low order of acute toxicity, had no major toxicologic findings in repeat-dose studies, was non-carcinogenic in 26-week Tg.rasH2 mouse and 2-year rat studies, and had no effect on fertility in rats.

Acute Toxicity

Azilsartan medoxomil has low oral acute toxicity in rats and dogs. Doses $\leq 2,000$ mg/kg were administered to rats and ≤ 30 mg/kg to dogs with no severe clinical signs or mortality. Transient diarrhea and vomiting occurred in dogs at ≤ 30 mg/kg. Severe clinical signs (including convulsions) occurred after intravenous bolus dosing of azilsartan medoxomil (≥ 40 mg/kg) in rats, with lethality at 40 mg/kg in males and 200 mg/kg in females.

Long Term Toxicity

Oral repeat-dose toxicity studies demonstrated that the NOAELs for azilsartan medoxomil occurred at < 20 mg/kg/day in mice (13 weeks), 20 (males) and 200 (females) mg/kg/day in rats (6 months), and 60 (males) and 12 (females) mg/kg/day in dogs (6 months). Severe toxicity, including mortality, occurred in dogs administered azilsartan medoxomil at 300 mg/kg/day (males) and ≥ 100 mg/kg/day (females). Following administration of 300 mg/kg/day (males) and 100 mg/kg/day (females) of azilsartan in the chronic dog study, systemic exposure to azilsartan at 6 months was about 7- fold (both males and females,) compared with exposure at the maximum recommended human dose (MRHD). Clinical and clinical pathology findings and pathologic lesions in several organs (including kidney, gastrointestinal tract and heart) reflected effects secondary to uremia and altered body fluid balance/poor general condition. Deaths were reported in mice at doses ≤ 200 mg/kg/day. No deaths occurred in rats administered $\geq 2,000$ mg/kg/day for 6 months.

Hematological effects in animals included decreases in erythroid parameters, such as erythrocyte count, hemoglobin concentration, and hematocrit value. Clinical chemistry changes included increases in blood urea nitrogen, creatinine, and total cholesterol, as well as decreased levels of triglycerides, sodium, chloride and calcium. Increased plasma/serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase occurred following administration of relatively high dose levels. Urinary excretion of sodium and chloride were decreased.

Histopathological findings in the stomach and kidneys of rodents and dogs, and in adrenals of rats were observed, including changes in the glandular stomach that were seen in mice, rats and dogs. In kidney,

hypertrophy or hyperplasia of the juxtaglomerular apparatus is considered to be due to the pharmacological effects of azilsartan on the RAAS. Renal tubular dilatation, basophilia, vacuolization and regeneration were observed in mice, rats, and dogs. These histopathological findings in kidneys (and in stomach in one rat study) occurred, in repeat-dose toxicity studies, at systemic exposure levels similar to the MRHD of 80 mg/day in humans. Atrophy of the adrenal cortex zona glomerulosa, considered to represent a pharmacologic effect, occurred in rats at systemic exposure values of azilsartan that were lower than at the MRHD of 80 mg/day. Reversibility of the adrenal zona glomerulosa atrophy was not evaluated in non-clinical studies. Decreased heart weights were also observed in rats and mice treated with repeated dose of azilsartan medoxomil.

Decreased red blood cell parameters and heart weight, and pathologic changes in kidneys and stomach are anticipated effects in animals secondary to antagonism at angiotensin II type 1 (AT1) receptors. These findings were eliminated or diminished as a result of saline supplementation in rats.

Mutagenicity

Azilsartan medoxomil, azilsartan, and M-II were positive for structural aberrations in the Chinese Hamster Lung Cytogenetic Assay. Azilsartan medoxomil, azilsartan, and M-II were devoid of genotoxic potential in the bacterial (Ames) mutagenicity assays; azilsartan was negative in the in vitro Chinese Hamster Ovary Cell forward mutation and mouse lymphoma tk locus gene mutation assays; and azilsartan medoxomil and azilsartan were negative in unscheduled DNA synthesis tests in rats, and in vivo mouse and/or rat bone marrow micronucleus assays.

Carcinogenicity

Azilsartan medoxomil was not carcinogenic when assessed in 26-week transgenic (Tg.rasH2) mouse (highest dose tested 450 mg/kg/day) and 2-year rat (highest dose tested 600 mg/kg/day) studies with systemic exposures to azilsartan 7 and 17 (male and female mice) and 25 and 28 (male and female rats) times the average exposure to azilsartan in humans given the MRHD (80 mg azilsartan medoxomil/day).

Reproduction Studies

There was no effect of azilsartan medoxomil on the fertility of male or female rats at oral doses $\leq 1,000$ mg/kg/day, at which systemic exposure (AUC) to azilsartan would be about 30x that at the azilsartan medoxomil MRHD of 80 mg/day.

In pre- and postnatal development studies in rats, adverse effects on pup viability, delayed incisor eruption, and dilatation of the renal pelvis along with hydronephrosis were seen when azilsartan medoxomil was administered to pregnant rats from gestation day 6 to lactation day 21 at 10 mg/kg/day (estimated exposure margin 4.5x the MRHD based on AUC data from non-pregnant rats). Similar studies with azilsartan in rats resulted in F1 generation findings of dilatation of the renal pelvis/ureter (≥ 0.3 mg/kg/day), lower body weight and survival, and increased incidence of rough kidney surface (≥ 10 mg/kg/day), and F1 reproductive effects (30 mg/kg/day).

Azilsartan medoxomil was not teratogenic when administered at oral doses $\leq 1,000$ mg/kg/day azilsartan medoxomil/kg/day to pregnant rats or ≤ 50 mg/kg/day azilsartan medoxomil to pregnant rabbits. However, embryo-fetal toxicity occurred at azilsartan medoxomil doses of 1,000 mg/kg/day in rats (dilated renal pelvis and short supernumerary ribs) and 50 mg/kg/day in rabbits (increased post-

implantation loss, embryo-fetal deaths, and decreased number of live fetuses), with azilsartan systemic exposure at the NOAELs (100 and 30 mg/kg/day, respectively) estimated at 20x and 9x that at the MRHD. Embryo-fetal toxicity was also reported in rats with azilsartan doses of ≥ 30 mg/kg/day (delayed ossification in the caudal vertebrae) and 100 mg/kg/day (lower male fetal body weight) and at 500 mg/kg/day in rabbits (increased post-implantation loss). Azilsartan crossed the placenta and was found in the fetuses of pregnant rats and was also excreted into the milk of lactating rats.

17. Supporting Product Monographs

1. PrEDARBI® Azilsartan Medoxomil Tablets, 40 mg and 80 mg, control 298416, product monograph, Bausch Health, Canada Inc. (2025-10-25)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **Auro-Azilsartan Medoxomil**

Azilsartan Medoxomil Tablets

This Patient Medication Information is written for the person who will be taking **Auro-Azilsartan Medoxomil**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Auro-Azilsartan Medoxomil**, talk to a healthcare professional.

Serious warnings and precautions box

- **Auro-Azilsartan Medoxomil should not be used during pregnancy. Taking Auro-Azilsartan Medoxomil during pregnancy can cause injury or even death to your baby.**
- **If you discover that you are pregnant while taking Auro-Azilsartan Medoxomil, stop the medication and contact your healthcare professional as soon as possible.**

What Auro-Azilsartan Medoxomil is used for:

Auro-Azilsartan Medoxomil is used in adults to lower high blood pressure. It can be used alone or together with a thiazide diuretic (“water pill”) or a calcium channel blocker.

How Auro-Azilsartan Medoxomil works:

Auro-Azilsartan Medoxomil is an angiotensin receptor blocker (ARB). It lowers blood pressure. This medicine does not cure your disease. It helps control it. Therefore, it is important to continue taking Auro-Azilsartan Medoxomil regularly even if you feel fine.

The ingredients in Auro-Azilsartan Medoxomil are:

Medicinal ingredients: azilsartan medoxomil

Non-medicinal ingredients: Croscarmellose sodium, HPMC 2910 / Hypromellose, hydroxy propyl cellulose, iron oxide yellow, macrogol/PEG, magnesium aluminometa silicate, magnesium stearate, mannitol, microcrystalline cellulose, talc and titanium dioxide.

Auro-Azilsartan Medoxomil comes in the following dosage forms:

Tablets: 40 mg and 80 mg

Do not use Auro-Azilsartan Medoxomil if:

- you are allergic to azilsartan medoxomil or to any other ingredients in Auro-Azilsartan Medoxomil.
- you have had an allergic reaction (angioedema) to any ARB. Signs of an allergic reaction include:
 - swelling of the hands, feet, ankles, face, lips, tongue and throat
 - suddenly having trouble breathing or swallowing
 Make sure that you tell your healthcare professional that this has happened to you before.
- you have diabetes or kidney disease and are already taking a blood pressure-lowering medicine that contains aliskiren.
- you are pregnant or intend to become pregnant. Taking Auro-Azilsartan Medoxomil during pregnancy can cause injury and even death to your baby.
- you are breastfeeding. It is possible that Auro-Azilsartan Medoxomil passes into breastmilk.

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

- have experienced an allergic reaction to any medicine used to lower blood pressure.
- have narrowing of an artery or a heart valve.
- have had a heart attack or stroke.
- have heart failure.
- have liver or kidney diseases.
- have diabetes.
- are on dialysis.
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- are on a low-salt diet.
- are taking a medicine that contains aliskiren.
- are taking an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in ‘-PRIL’.
- are 75 years of age or older. You are at a higher risk of experiencing low blood pressure while taking Auro-Azilsartan Medoxomil. Your healthcare professional will decide if Auro-Azilsartan Medoxomil is right for you.

Other warnings you should know about:

Auro-Azilsartan Medoxomil can cause serious side effects, including:

- **Hypotension (low blood pressure):** You may feel dizzy or light-headed:
 - Particularly in the first few days after you start taking Auro-Azilsartan Medoxomil or when your dose is increased.
 - When you exercise or when the weather is hot.
 You should lie down if this happens. If you faint, talk to your healthcare professional right away.
- **Allergic reactions (angioedema):** Some patients have reported experiencing allergic reactions (angioedema) while taking angiotensin receptor blockers (ARBs) such as azilsartan medoxomil. If you experience signs or symptoms of an allergic reaction while taking Auro-Azilsartan Medoxomil, stop taking it and tell your healthcare professional **right away**.

- **Kidney Disorder:** Auro-Azilsartan Medoxomil may cause kidney problems. Some patients experienced a decrease in urination, kidney injury or failure while taking ARBs such as azilsartan medoxomil. Some cases have resulted in death. If you experience signs or symptoms of kidney problems, tell your healthcare professional **right away**.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Driving and using machines: Before doing tasks that require special attention, wait until you know how you respond to Auro-Azilsartan Medoxomil. Dizziness, light-headedness, or fainting can occur, particularly in the first few days after you start taking Auro-Azilsartan Medoxomil or when your dose is increased.

Surgery: Tell your healthcare professional you are taking Auro-Azilsartan Medoxomil before undergoing any surgeries that require general anesthesia. This includes dental surgery. General anesthesia may cause a sudden fall in blood pressure.

Laboratory tests and monitoring: Your healthcare professional may do blood tests before you take Auro-Azilsartan Medoxomil and/or during treatment. This is to make sure your kidneys are working properly.

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 Auro-Azilsartan Medoxomil:

- Medicines that can increase the levels of potassium in your blood. These include:
 - potassium-sparing diuretics (a specific kind of “water pill”)
 - potassium supplements
 - salt substitutes that contain potassium
- Medicines that lower your blood pressure. These include:
 - Angiotensin-Converting Enzyme (ACE) inhibitors
 - aliskiren-containing medicines
 - diuretics (“water pills”)
- Amlodipine – used to treat high blood pressure and manage a type of chest pain called angina
- Lithium – used to treat bipolar disease
- Fluconazole, ketoconazole – used to treat fungal infections
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as ibuprofen, naproxen and celecoxib – used to reduce pain and swelling

How to take Auro-Azilsartan Medoxomil:

- Take Auro-Azilsartan Medoxomil every day exactly as prescribed.
- It is recommended to take your dose at about the same time every day.
- Auro-Azilsartan Medoxomil may be taken with or without food.

Usual dose:

- 40 mg tablet once a day.

- Your healthcare professional can increase the dosage to 80 mg once daily if required.

Overdose:

If you think you, or a person you are caring for, have taken too much Auro-Azilsartan Medoxomil, contact a healthcare professional, hospital emergency department regional poison control centre or Health Canada's toll free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or 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 the dose.

Possible side effects from using Auro-Azilsartan Medoxomil:

These are not all the possible side effects you may have when taking Auro-Azilsartan Medoxomil. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- Dizziness
- Fatigue
- Rash
- Itchy skin
- Hives
- Diarrhea
- Constipation
- Feeling sick
- Vomiting
- Headache
- Back pain
- Pain in your arms or legs
- Muscle pain or spasms
- Joint pain
- Vertigo
- Abdominal discomfort or pain
- Dry mouth
- Heartburn
- Toothache
- Anxiety
- Cough
- Sore throat
- Sinus congestion
- Excessive sweating
- Frequent urination
- Inflammation of the nose and throat
- Impotence (not able to have an erection)

Auro-Azilsartan Medoxomil can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them

| Frequency/Side Effect/Symptom | Talk to your healthcare professional | | Stop taking this drug and get immediate medical help |
|--|--------------------------------------|--------------|--|
| | Only if severe | In all cases | |
| Common | | | |
| Hyperkalemia (increased levels of potassium in the blood): irregular heartbeats, muscle weakness and generally feeling unwell | | √ | |
| Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up) | √ | | |
| Irregular heartbeat | √ | | |
| Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine | √ | | |
| Uncommon | | | |
| Allergic reactions (angioedema): difficulty swallowing or breathing; swollen face, hands and feet, genitals, tongue, throat; wheezing; hives or rash; swelling of the digestive tract causing diarrhea, nausea or vomiting | | | √ |
| Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue | | √ | |
| Liver Disorder: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness | | √ | |
| Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff | √ | | |
| Rare | | | |
| Rhabdomyolysis: muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine | | √ | |
| Very rare | | | |
| Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness | | √ | |
| Decreased Platelets: bruising, bleeding, fatigue and weakness | | √ | |
| Leukopenia (decreased white blood cells) – infections, fatigue, fever, aches, pains and flu-like symptoms | | √ | |
| Unknown | | | |
| Intestinal angioedema (swelling of the intestine): colicky abdominal pain, diarrhea, nausea or vomiting | | √ | |

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.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (<https://canada.ca/drug-device-reporting>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Store Auro-Azilsartan Medoxomil tablets between 15 to 30°C.
- Keep container tightly closed.
- Protect from light and moisture.
- Keep tablets in original packaging. Do not transfer Auro-Azilsartan Medoxomil tablets to a different container.
- Keep out of reach and sight of children.

If you want more information about Auro-Azilsartan Medoxomil:

- 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 Drug Product Database website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <http://www.auropharma.ca>, or by calling 1-855-648-6681.

This leaflet was prepared by Auro Pharma Inc.

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