PRODUCT MONOGRAPH

PrEDARBI®

azilsartan medoxomil (as azilsartan medoxomil potassium)

Tablets, 40 mg and 80 mg

Angiotensin II AT_1 Receptor Blocker

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet 40 mg, 80 mg	Croscarmellose sodium, fumaric acid, hydroxypropyl cellulose, mannitol, magnesium stearate, microcrystalline cellulose, and sodium hydroxide.

INDICATIONS AND CLINICAL USE

EDARBI® (azilsartan medoxomil) is an angiotensin II receptor blocker (ARB) indicated for the treatment of mild to moderate essential hypertension.

EDARBI® may be used alone or concomitantly with thiazide diuretics or calcium channel blockers.

Geriatrics (≥ 65 years of age):
No initial dose adjustment with EDARBI® 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.

Pediatrics (< 18 years of age):
Safety and efficacy in pediatric patients have not been established. Therefore, EDARBI® is not indicated in this patient population.

CONTRAINDICATIONS

EDARBI® (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 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/1.73m^2) (see WARNINGS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs).

- Pregnant women (see WARNINGS AND PRECAUTIONS, **Special Populations**, **Pregnant Women**).
- Nursing women (see WARNINGS AND PRECAUTIONS, **Special Populations**, **Nursing Women**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, EDARBI® (azilsartan medoxomil) should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

Cardiovascular

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin-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 EDARBI®. The condition should be corrected prior to administration of EDARBI®, 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 EDARBI®, 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/1.73m^2). Therefore, the use of EDARBI® in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ARBs, including EDARBI®, 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.

Hepatic/Biliary/Pancreatic

EDARBI® 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 EDARBI® 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 ACTION AND CLINICAL PHARMACOLOGY).

Immune

Angioedema

One case of angioedema was reported and possibly related to the use of EDARBI®. Angioedema has been reported with other ARBs. There is a potential risk of angioedema with the use of EDARBI®. If angioedema of the face, extremities, lips, tongue, or glottis occurs, EDARDI® 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 EDARBI®.

Renal

As a consequence of inhibiting the RAAS, changes in renal function may be anticipated in susceptible individuals treated with EDARBI®. 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 EDARBI® (see ACTION AND CLINICAL PHARMACOLOGY).

The use of ARBs – including EDARBI® – or ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). (See CONTRAINDICATIONS and 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 EDARBI® in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected with the use of EDARBI®.

Use of EDARBI® 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 EDARBI® in these patients. No dose adjustment is required in patients with mild or moderate renal impairment (see ACTION AND CLINICAL PHARMACOLOGY).

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

Special Populations

Pregnant Women:
Drugs that act directly on RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, EDARBI® should be discontinued as soon as possible.

The use of ARBs is contraindicated during pregnancy (see 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 EDARBI®. 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, hyperkalaemia).

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.

Nursing Women:
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 CONTRAINDICATIONS).

Pediatrics (< 18 years of age):
Safety and efficacy in pediatric patients have not been established. Therefore, EDARBI® is not indicated in this patient population.

Geriatrics (> 65 years of age):
No initial dose adjustment with EDARBI® 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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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

EDARBI® (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 EDARBI® 40 mg, and 2.7% (29/1074) for EDARBI® 80 mg.

In the placebo-controlled monotherapy studies, treatment-emergent AEs occurring at an incidence of ≥1% in patients treated with EDARBI® are presented in Table 1.

Table 1. Treatment-Emergent Adverse Events Occurring in ≥ 1% of Patients

Adverse Events	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			
Dyslipidaemia	6 (1.4%)	19 (2.7%)	23 (3.3%)
Hypertriglyceridaemia	4 (0.9%)	8 (1.1%)	8 (1.1%)
Gastrointestinal			
Diarrhoea	2 (0.5%)	11 (1.6%)	17 (2.4%)
Nausea	2 (0.5%)	7 (1.0%)	8 (1.1%)

Adverse Events	Placebo (n=435) Case (%)	Azilsartan medoxomil 40 mg (n=698) Case (%)	Azilsartan medoxomil 80 mg (n=704) Case (%)
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%)

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

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
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

Abnormal Hematologic and Clinical Chemistry Findings

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

Blood creatine phosphokinase: High levels of creatine phosphokinase were observed in 0.3% of patients treated with EDARBI® and 0.3% of patients treated with placebo.

Serum creatinine: Small reversible increases in serum creatinine were seen in patients receiving EDARBI®. The increase may be larger when coadministered with chlorthalidone or hydrochlorothiazide. In addition, patients taking EDARBI® 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 aminotransferease (ALT), aspartate aminotransferase (AST), and blood uric acid were seen in <1% of patients treated with EDARBI®.

Hemoglobin and Hematocrit: Low hemoglobin, hematocrit, and red blood cell (RBC) counts were observed in 0.2%, 0.4%, and 0.3% of EDARBI®-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.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during the post-approval use of EDARBI®. 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
Musculoskeletal and Connective Tissue Disorders: Muscle spasms
Skin and subcutaneous Tissue Disorders: Angioedema, Pruritus, Rash

DRUG INTERACTIONS

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).

Table 2. Established or Potential Drug-Drug Interaction

Common Name	Reference	Effect	Clinical Comments
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.
Antacid	CT	In a short-term study, concomitant administration azilsartan medoxomil and antacid liquid results in a small (18%) decrease in $AUC_{(0\text{-}inf)}$ of azilsartan and T_{max} delay for 1.5 hour. There is no change in azilsartan C_{max}.	-

Common Name	Reference	Effect	Clinical Comments
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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).

Common Name	Reference	Effect	Clinical Comments
Fluconazole	CT	Concomitant administration of azilsartan and fluconazole (a potent CYP2C9/CYP2C19 inhibitor) increases azilsartan plasma $AUC_{(0\text{-}inf)}$ by 42%, C_{max} by 14%, and urinary exposure $XU_{(0\text{-}24)}$ 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 $AUC_{(0\text{-}inf)}$ 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.
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}.	-

Common Name	Reference	Effect	Clinical Comments
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}.	-
CT = Clinical Trial; C: Case Study; T = Theoretical			

Drug-Food Interactions

EDARBI® may be taken with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

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.

EDARBI® may be taken with or without food.

Dosing Considerations

Geriatrics:
No initial dose adjustment with EDARBI® 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:
EDARBI® 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 EDARBI® 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 EDARBI® 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.

Missed Dose

If a dose of EDARBI® 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.

OVERDOSAGE

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

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

overdosage would be hypotension and tachycardia. Bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension should occur, supportive treatment should be initiated.

Hemodialysis does not remove azilsartan from the systemic circulation.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Azilsartan medoxomil, a prodrug, is hydrolyzed to azilsartan during absorption from the gastrointestinal tract. Azilsartan is a selective AT_1 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 AT_1 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 AT_2 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 AT_1 receptor than for the AT_2 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.

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 EDARBI® 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 EDARBI® 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.

Pharmacokinetics

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; $AUC_{0\text{-}inf}$ is presented for single dose and $AUC_{0\text{-}tau}$ is presented for multiple dose.
ND: Not determined.

Absorption: Azilsartan medoxomil is rapidly hydrolyzed to azilsartan, a selective antagonist of angiotensin AT_1 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 EDARBI®. The major enzyme responsible for azilsartan metabolism is CYP2C9.

Excretion: Following an oral dose of ^{14}C-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 (< 18 years of age): Pharmacokinetics of azilsartan has not been studied in patients <18 years of age.

Geriatrics (> 65 years of age): Pharmacokinetics of azilsartan do not differ significantly between young (age range 18-45) and elderly (age range 65-85) subjects.

Gender: Pharmacokinetics of azilsartan do not differ significantly between males and females. No dose adjustment is necessary based on gender.

Race: Pharmacokinetics of azilsartan do not differ significantly between the black and white populations.

Hepatic Impairment:
EDARBI® 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 Impairment: 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.

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

Do not repackage EDARBI®. Dispense and store EDARBI® in its original container with provided desiccant to protect EDARBI® from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

EDARBI® is supplied as white to nearly white round tablets in the following dosage strengths:

- 40 mg tablets - debossed “ASL” on one side and “40” on the other
- 80 mg tablets - debossed “ASL” on one side and “80” on the other

EDARBI® is available for oral use as tablets. Each EDARBI® tablet contains 42.68 mg or 85.36 mg of azilsartan medoxomil potassium, which is equivalent to containing 40 mg or 80 mg respectively, of azilsartan medoxomil and the following non-medicinal ingredients: croscarmellose sodium, fumaric acid, hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose and sodium hydroxide.

EDARBI® tablets are supplied in high-density polyethylene (HDPE) bottles of 30 or 90 count tablets and cartons containing 1 blister of 7 tablets or 2 blisters of 14 tablets each.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: azilsartan medoxomil

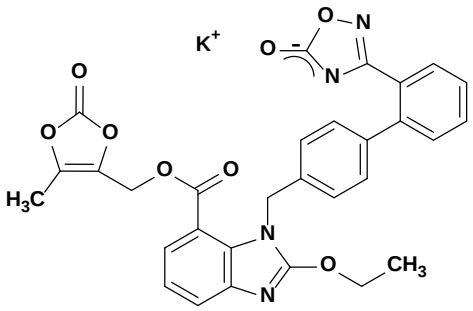
Chemical name: (5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylate monopotassium salt.

Molecular formula and molecular mass:

Azilsartan medoxomil potassium ($C_{30}H_{23}KN_4O_8$): 606.62

Azilsartan medoxomil: 568.53

Structural formula:



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

CLINICAL TRIALS

Study demographics and trial design

Table 4: Study Demographics and Trial Design

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

Study Results

Two 6-week randomized, double blind studies (Study 1 and Study 2) compared the efficacy on blood pressure of EDARBI® 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 hour mean blood pressure by ambulatory blood pressure monitoring (ABPM) are shown in Table 5 for both studies. EDARBI® was statistically superior to placebo for both clinic and 24 hour mean blood pressure measurements.

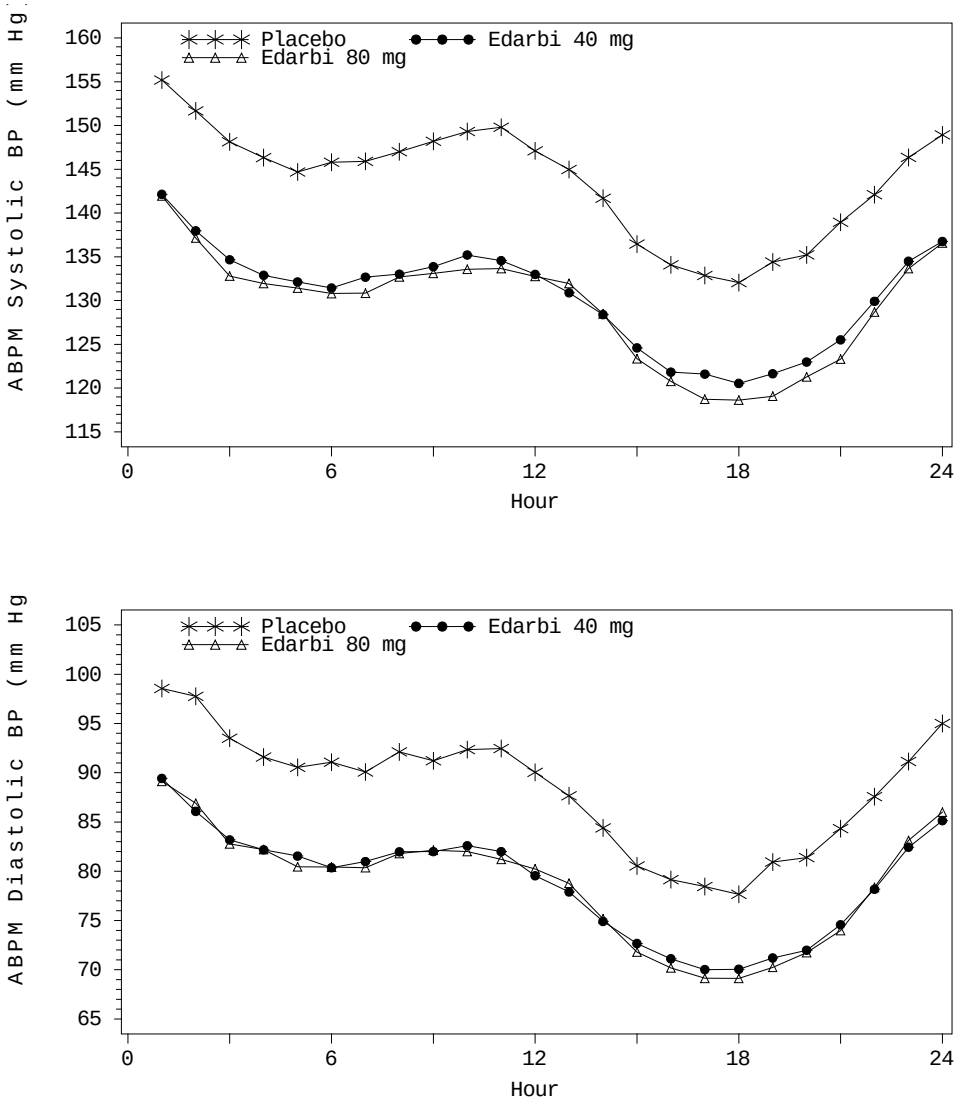
Table 5: Placebo-Corrected Mean Change from Baseline in Systolic / Diastolic Blood Pressure at 6 Weeks (mm Hg)

	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)
EDARBI® 40 mg	-14.6 / -6.2	-13.2 / -8.6	-12.4 / -7.1	-12.1 / -7.7
EDARBI® 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. EDARBI® 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.

EDARBI® 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.

EDARBI® 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 EDARBI® 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 EDARBI® 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.

DETAILED PHARMACOLOGY

Pharmacodynamics

The results of nonclinical pharmacology studies demonstrated that azilsartan, the active form of azilsartan medoxomil, is a long-lasting, competitive, reversible and selective antagonist at the angiotensin II receptor AT1. Azilsartan medoxomil and azilsartan dose-dependently reduced blood pressure in animal models of normo- and supra-renin hypertension. Two metabolites of azilsartan, M-I and M-II, demonstrated only weak binding affinity for AT1 receptors and are pharmacologically inactive.

Binding and functional assays showed that the secondary pharmacodynamic effects of azilsartan medoxomil and related compounds/metabolites occurred at concentrations ≥10x higher than that would be anticipated with an 80 mg dose in human.

In safety pharmacology studies, azilsartan medoxomil did not adversely affect the central nervous system or respiratory function in rats (≤2,000 mg/kg p.o.), or cardiovascular parameters (other than the expected decrease in arterial blood pressure) in dogs (≤ 300 mg/kg p.o.). Results of *in vitro* study did not indicate potential for inhibition of hERG channel current by azilsartan.

Pharmacokinetics

Based on the *in vitro* data using Caco-2 cell monolayers, neither azilsartan medoxomil nor azilsartan is considered as a potential P-glycoprotein substrate or inhibitor in the clinical setting.

After a single oral dose of radioactive azilsartan medoxomil in rats, total radioactivity was distributed widely to tissues with relatively high concentrations in liver. Azilsartan is highly protein bound in plasma of animals and humans.

Azilsartan is metabolized into the inactive metabolites M-I and M-II, primarily by the cytochrome P450 (CYP) isoform CYP2C8 and CYP2C9, respectively. Only a small amount of unchanged azilsartan was present in urine or feces. In human hepatic microsomes, azilsartan medoxomil was found to inhibit CYP2C8 and CYP2C9 with IC_{50} <10 µmol/L, whereas, in human hepatocytes, azilsartan did not affect any of the CYPs tested.

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 ≤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 medoximil 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 ≤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 (AT_1) 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 ≤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 ≤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.

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2. White WB, Weber MA, Sica D, Bakris GL, Perez A, Cao C, Kupfer S. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinical blood pressure in patients with stages 1 and 2 hypertension. Hypertens 2011; 57:413-420.
3. Sica D, White WB, Weber MA, Bakris GL, Perez AP, Cao C, Handley A, Kupfer S. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. J Clin Hypertens (Greenwich). 2011; 13:467-72.

PART III: CONSUMER INFORMATION

[Pr]EDARBI®
azilsartan medoxomil tablets

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

ABOUT THIS MEDICATION

What the medication is used for:
EDARBI® lowers high blood pressure in adults.

EDARBI® may be used alone, or along with thiazide diuretics, or calcium channel blockers.

What it does:
EDARBI® is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN".

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

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

What the medicinal ingredient is:
azilsartan medoxomil

What the nonmedicinal ingredients are:
Croscarmellose sodium, fumaric acid, hydroxypropyl cellulose, mannitol, magnesium stearate, microcrystalline cellulose, and sodium hydroxide.

What dosage forms it comes in:
Tablets, 40 mg and 80 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions – Pregnancy
EDARBI® should not be used during pregnancy. If you discover that you are pregnant while taking EDARBI®, stop the medication and contact your doctor, nurse or pharmacist as soon as possible.

BEFORE you use EDARBI®, talk to your doctor, nurse, or pharmacist if you:
- Have experienced an allergic reaction to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors.
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure.
- Have diabetes, liver or kidney diseases.
- Are on dialysis.
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- 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 on a low-salt diet.
- Are taking a medicine that contains aliskiren, such as Rasilez®, used to lower high blood pressure. The combination with EDARBI® is not recommended.
- Are taking an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in **'-PRIL'.**
- Are less than 18 years old.

Driving and using machines: Before doing tasks which require special attention, wait until you know how you respond to EDARBI®. Being dizzy, lightheaded, or fainting can occur. Take care especially after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

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

The following may interact with EDARBI®:
- Amlodipine used to lower high blood pressure or manage a type of chest pain called angina.
- 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").
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprophen, naproxen and celecoxib.
- Medications used to treat fungal infections, such as fluconazole and ketoconazole.

- Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez®), or angiotensin converting enzyme (ACE) inhibitors.

PROPER USE OF THIS MEDICATION

Take EDARBI® exactly as prescribed. It is recommended to take your dose at about the same time every day. EDARBI® can be taken with or without food.

Usual adult dose:

The recommended dose is one 40 mg tablet once a day. If your blood pressure is not well controlled, your doctor may increase the dose to 80 mg, and/or decide to add another medicine.

Overdose:

If you think you have taken too much of EDARBI® contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- dizziness
- drowsiness, insomnia, fatigue
- rash
- diarrhea, nausea, vomiting
- headache
- back or leg pain, muscle cramps

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

EDARBI® can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness	✓		
	Increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		✓	
	Irregular heartbeat	✓		
	Urinary Tract Infection: increased frequency, urgency, pain when urinating, blood in the urine	✓		
Uncommon	**Allergic Reaction (angioedema):** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	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		✓	
	Peripheral edema: swelling of the legs and feet	✓		
Rare	**Rhabdomyolysis:** muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		✓	
Very rare	**Decreased Platelets:** bruising, bleeding, fatigue and weakness		✓	

This is not a complete list of side effects. For any unexpected effects while taking EDARBI®, contact your doctor, nurse or

pharmacist.

HOW TO STORE IT

EDARBI® should be protected from light and moisture.
Store EDARBI® at 15 - 30° C.

Keep EDARBI® in the original container that you received from your pharmacist, nurse or doctor. Do not transfer EDARBI® to a different bottle or container.

Keep EDARBI® and all medicines out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Valeant Canada LP at: 1-800-361-4261.

This leaflet was prepared by

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