AZEARLY® Tablets

Each Tablet Contains

Azilsartan – 20/40/80 mg

PHARMACEUTICAL INFORMATION –

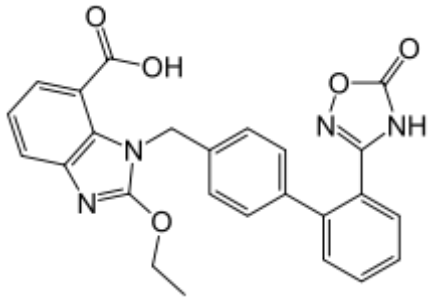
AZILSARTAN

Generic name: Azilsartan

Chemical name: 2-Ethoxy-1-{[2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-4-biphenylyl]methyl}-1*H*-benzimidazole-7-carboxylic acid

Molecular mass: 456.46 g/mol

Structural formula:



Empirical formula – $C_{25}H_{20}N_4O_5$

Storage and Stability:

PHARMACOKINETIC PROPERTIES –

Azilsartan

Absorption

Azilsartan medoxomil is hydrolyzed to azilsartan, the active metabolite, in the gastrointestinal tract during absorption. Azilsartan medoxomil is not detected in plasma after oral administration. Dose proportionality in exposure was established for azilsartan in the azilsartan medoxomil dose range of 20 mg to 320 mg after single or multiple dosing. The estimated absolute bioavailability of azilsartan following administration of azilsartan medoxomil is approximately 60 %. After oral administration of azilsartan medoxomil, peak plasma concentrations (Cmax) of azilsartan are reached within 1.5 to 3 hours. Food does not affect the bioavailability of azilsartan. Distribution volume of distribution of azilsartan is approximately 16

L. 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 passed across the placental barrier in pregnant rats and was distributed to the fetus.

Metabolism and Elimination

Azilsartan is metabolized to two primary metabolites. The major metabolite in plasma is formed by Ode alkylation, 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 less than 1 % of azilsartan, respectively. M-I and M-II do not contribute to the pharmacologic activity of AZEARLY. The major enzyme responsible for azilsartan metabolism is CYP2C9. 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 five days, and no accumulation in plasma occurs with repeated once-daily dosing.

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION –

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, 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 more than a 10,000-fold greater affinity for the AT1 receptor than for the AT2 receptor. Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction catalyzed by ACE. Because azilsartan does not inhibit ACE (kinase II), it should not affect bradykinin levels. Whether this difference has clinical relevance is not yet known. Azilsartan does not bind to or block other receptors or ion channels known to be important in cardiovascular regulation. 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 levels do not overcome the effect of azilsartan on blood pressure.

INDICATION –

AZEARLY is an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension to lower blood pressure. AZEARLY may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS –

Do not co-administer aliskiren with AZEARLY in patients with diabetes

DOSAGE AND ADMINISTRATION –

AZEARLY Tab– 20/40/80 mg OD

ADVERSE EFFECTS –

- Nausea
- Muscle spasms
- Rash
- Pruritus
- Angioedema

OVERDOSAGE

Limited data are available related to overdosage in humans. During controlled clinical trials in healthy subjects, once-daily doses up to 320 mg of AZEARLY were administered for seven days and were well tolerated. In the event of an overdose, supportive therapy should be instituted as dictated by the patient's clinical status. Azilsartan is not dialyzable.

WARNINGS AND PRECAUTIONS

Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue AZEARLY as soon as possible.

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may

occur after initiation of treatment with AZEARLY. Correct volume or salt depletion prior to administration of AZEARLY, or start treatment at 40 mg. 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.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin system, changes in renal function may be anticipated in susceptible individuals treated with AZEARLY. In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g., patients with severe congestive heart failure, renal artery stenosis, or volume depletion), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been associated with oliguria or progressive azotemia and rarely with acute renal failure and death. Similar results may be anticipated in patients treated with AZEARLY. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. There has been no long-term use of AZEARLY in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

DRUG INTERACTIONS –

No clinically significant drug interactions have been observed in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, chlorthalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, pioglitazone, and warfarin. Therefore, AZEARLY may be used concomitantly with these medications.

Special Populations

Pregnancy

Pregnancy Category D

Use of drugs that affect the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue AZEARLY as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother

and fetus. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue AZEARLY, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to AZEARLY for hypotension, oliguria, and hyperkalemia.

Nursing Mothers

It is not known if azilsartan is excreted in human milk, but azilsartan is excreted at low concentrations in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Neonates with a history of in utero exposure to AZEARLY If oliguria or hypotension occurs, support blood pressure and renal function. Exchange transfusions or dialysis may be required. Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric

Use No dose adjustment with AZEARLY is necessary in elderly patients. Of the total patients in clinical studies with AZEARLY, 26% were elderly (65 years of age and older); 5% were 75 years of age and older. Abnormally high serum creatinine values were more likely to be reported for patients age 75 or older. No other differences in safety or effectiveness were observed between elderly patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

Dose adjustment is not required in patients with mild-to-severe renal impairment or end-stage renal disease. Patients with moderate to severe renal impairment are more likely to report abnormally high serum creatinine values.

Hepatic Impairment

No dose adjustment is necessary for subjects with mild or moderate hepatic impairment. It has not been studied in patients with severe hepatic impairment.

SHELF-LIFE -

PACKAGING INFORMATION -