Azilura™ 40/80

WARNING: TO BE SOLD BY RETAIL ON THE PRESCRIPTION OF CARDIOLOGIST ONLY

AZILSARTAN MEDOXOMIL TABLETS 40 mg & 80 mg

Azilura™ 40/80 अज़ीलूरा ४० / ८०

WARNING: FETAL TOXICITY
- When pregnancy is detected, discontinue Azilsartan medoxomil as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Composition

Azilura™ 40 अज़ीलूरा ४०

Each uncoated tablet contains
Azilsartan Kamedoxomil
Equivalent to Azilsartan medoxomil 40mg

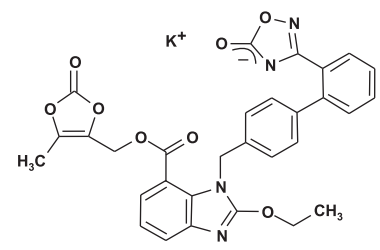
Azilura™ 80 अज़ीलूरा

Each uncoated tablet contains
Azilsartan Kamedoxomil
Equivalent to Azilsartan medoxomil 80mg

DESCRIPTION

Azilsartan medoxomil, a prodrug, is hydrolyzed to azilsartan in the gastrointestinal tract during absorption. Azilsartan is a selective AT1 subtype angiotensin II receptor antagonist.
The drug substance used in the drug product formulation is the potassium salt of azilsartan medoxomil, also known by the US accepted name of azilsartan kamedoxomil and is chemically described as (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.

Its empirical formula is $C_{30}H_{23}KN_4O_8$ and its structural formula is:



Azilsartan kamedoxomil is a white to nearly white powder with a molecular weight of 606.62. It is practically insoluble in water and freely soluble in methanol.
Azilsartan is available for oral use as tablets. Each Azilsartan tablet contains 42.68 or 85.36 mg of azilsartan kamedoxomil, which is equivalent to containing 40 mg or 80 mg respectively, of azilsartan medoxomil and the following inactive ingredients: mannitol, fumaric acid, sodium hydroxide, hydroxypropyl cellulose, croscarmellose sodium, microcrystalline cellulose, and magnesium stearate.

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg and 80 mg

INDICATIONS AND USAGE

Azilsartan is an angiotensin II receptor blocker indicated for the treatment of hypertension in adult patients, either alone or in combination with other antihypertensive agents.

DOSAGE AND METHOD OF ADMINISTRATION

Recommended Dose

The recommended dose in adults is 80 mg taken orally once daily. Consider a starting dose of 40 mg for patients who are treated with high doses of diuretics.
If blood pressure is not controlled with Azilsartan alone, additional blood pressure reduction can be achieved by taking Azilsartan with other antihypertensive agents.
Azilsartan may be taken with or without food.

Handling Instructions

Do not repackage Azilsartan. Dispense and store Azilsartan in its original container to protect Azilsartan from light and moisture.

Special Populations

No initial dose adjustment is recommended for elderly patients, patients with mild-to-severe renal impairment, end-stage renal disease, or mild-to-moderate hepatic dysfunction. Azilsartan has not been studied in patients with severe hepatic impairment.

USE IN SPECIFIC 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 Azilsartan 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 Azilsartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and cardiologist 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 Azilsartan 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 Azilsartan

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 Azilsartan is necessary in elderly patients. Of the total patients in clinical studies with Azilsartan, 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. Azilsartan has not been studied in patients with severe hepatic impairment.

CONTRAINDICATIONS

Do not coadminister aliskiren with Azilsartan in patients with diabetes.

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 Azilsartan 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 Azilsartan. Correct volume or salt depletion prior to administration of Azilsartan, 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 Azilsartan. 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 Azilsartan.
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 Azilsartan 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, azilsartan may be used concomitantly with these medications

Non-steroidal Anti-Inflammatory Agents, including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including azilsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving azilsartan and NSAID therapy.
The antihypertensive effect of angiotensin II receptor antagonists, including azilsartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on azilsartan and other agents that affect the RAS.
Do not coadminister aliskiren with azilsartan in patients with diabetes. Avoid use of aliskiren with azilsartan in patients with renal impairment (GFR <60 mL/min).

Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor agonists. Monitor serum lithium levels during concomitant use.

Undesirable effects

Clinical Trials Experience

As far as safety is concerned, both the study drugs (Azilsartan medoxomil 40 mg, Azilsartan medoxomil 80 mg) were equally tolerated and there were no in the incidence of treatment related adverse events. None of the treatment population had reported any adverse events. There was no death occurred during the study. No Treatment-Emergent Adverse Events (TEAEs) were reported in the study. There was no Serious

Adverse Event (SAE) reported through out of the study.
With respect to laboratory finding there were relatively unchanged mean values for liver function test and renal function tests. Same also found in case of other laboratory finding like routine hematology and hematocrit.
There were no notable changes in urine analysis parameters, vital signs, physical examination, and systemic examination.
The following adverse reactions have been identified during the post marketing use of reference product [EDARBI (Azilsartan medoxomil 40 mg, Azilsartan medoxomil 80 mg)]
- Nausea
- Muscle spasms
- Rash
- Pruritus
- Angioedema

Overdose
Limited data are available related to overdosage in humans.

PHARMACOLOGY

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

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. Plasma angiotensin I and II concentrations and plasma renin activity increased while plasma aldosterone concentrations decreased after single and repeated administration of Azilsartan to healthy subjects; no clinically significant effects on serum potassium or sodium were observed.

Effect on Cardiac Repolarization
A thorough QT/QTc study was conducted to assess the potential of azilsartan to prolong the QT/QTc interval in healthy subjects. There was no evidence of QT/QTc prolongation at a dose of 320 mg of azilsartan.

Pharmacokinetics

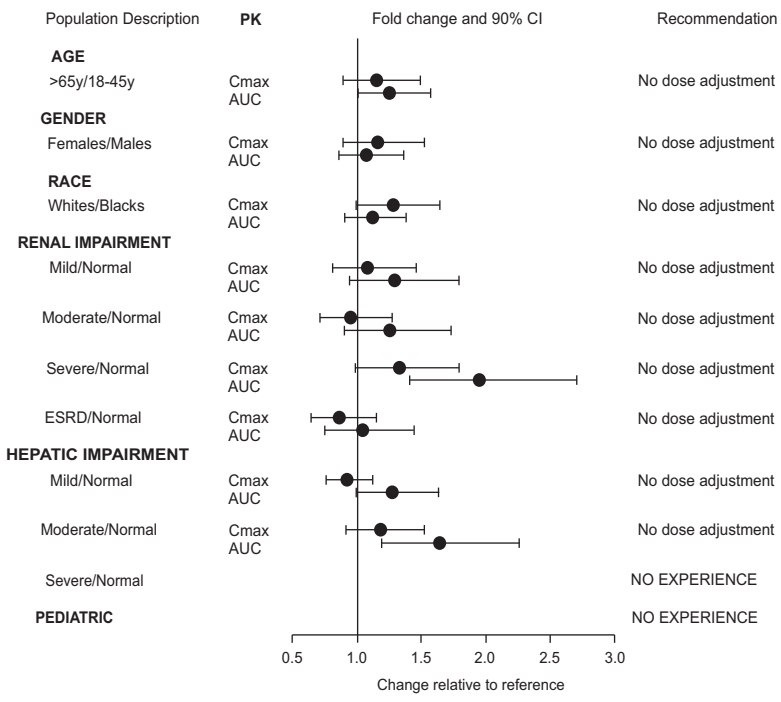
Absorption
Azilsartan medoxomil is hydrolyzed to azilsartan, the active metabolite, in the gastrointestinal tract during absorption. Azilsartan medoxomil is not detected in plasma after oral administration. Dose proportionality in exposure was established for azilsartan in the azilsartan medoxomil dose 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
The 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 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 less than 1% of azilsartan, respectively. M-I and M-II do not contribute to the pharmacologic activity of Azilsartan. 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.

Special Populations
The effect of demographic and functional factors on the pharmacokinetics of azilsartan was studied in single and multiple dose studies. Pharmacokinetic measures indicating the magnitude of the effect on azilsartan are presented in Figure 1 as change relative to reference (test/reference). Effects are modest and do not call for dosage adjustment.

Figure 1. Impact of intrinsic factors on the pharmacokinetics of azilsartan



Packaging information
Azilsartan Medoxomil Tablets 40 mg - 10's Alu-Alu Blister pack
Azilsartan Medoxomil Tablets 80 mg - 10's Alu-Alu Blister pack

Storage
Store below 25°C.
Protect from light and moisture.

Keep out of reach of children
Keep Azilsartan and all medicines out of the reach of children.

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325, Telangana, INDIA.

TM Trade mark under registration

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