ZILANCE Tablets (Azilsartan medoxomil)

Composition

ZILANCE 40
Each tablet contains:
Azilsartan kamedoxomil equivalent to Azilsartan medoxomil....40 mg
Excipients....q.s

ZILANCE 80
Each tablet contains:
Azilsartan kamedoxomil equivalent to Azilsartan medoxomil....80 mg
Excipients....q.s

Dosage Form

Tablets

Pharmacology

Pharmacodynamics

Azilsartan is a selective AT₁ subtype angiotensin II receptor antagonist.

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 (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 more than a 10,000-fold greater affinity for the AT₁ receptor than for the AT₂ receptor.

Blockade of the RAS 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 (BP).
**Pressor Effects**
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 medoxomil 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 ($C_{\text{max}}$) 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**
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.

**Elimination**
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 five days, and no accumulation in plasma occurs with repeated once-daily dosing.

### Indication

ZILANCE is indicated for the treatment of hypertension in adult patients, either alone or in combination with other antihypertensive agents.

### Dosage And Administration
The recommended dose in adults is one tablet of ZILANCE 80 taken orally once daily. Consider a starting dose of one tablet of ZILANCE 40 for patients who are treated with high doses of diuretics. If BP is not controlled with ZILANCE alone, additional BP reduction can be achieved by taking ZILANCE with other antihypertensive agents. ZILANCE is for oral use and may be taken with or without food.

### Special Populations

**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.

**Pediatric Population:** Safety and effectiveness in pediatric patients under 18 years of age have not been established in pediatric patients.

**Neonates with a history of in utero exposure to azilsartan.**

If oliguria or hypotension occurs, support BP and renal function. Exchange transfusions or dialysis may be required.

**Geriatric Population:** No dose adjustment with azilsartan is necessary in elderly patients. Abnormally high serum creatinine values are 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 is observed.

**Intravascular Volume Depletion:** For patients with possible depletion of intravascular volume or salt depletion (e.g. patients with vomiting, diarrhea or taking high doses of diuretics), azilsartan should be initiated under close medical supervision and consideration can be given to 20 mg as a starting dose.

### Contraindications

Hypersensitivity to azilsartan or any of the excipients of the product

Second and third trimester of pregnancy

The concomitant use of azilsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment

### Warnings And Precautions

**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 (NSAIDs), 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, coadministration 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 blockers, including azilsartan, may be attenuated by
NSAIDs, including selective COX-2 inhibitors.

**Dual Blockade of RAS**

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and BP.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

**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.

**Additional Information**

Clinical trial data has shown that dual blockade of the RAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAS-acting agent.

### Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated RAS, such as volume- and/or salt-depleted patients (e.g., patients with vomiting or diarrhea or 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 BP has stabilized.

### Primary Hyperaldosteronism

Patients with primary hyperaldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the RAS. Therefore, the use of azilsartan is not recommended in these patients.

### Hyperkalemia

Based on experience with the use of other medicinal products that affect the RAS, concomitant use of azilsartan with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium in hypertensive patients. In the elderly, in patients with renal insufficiency, in diabetic patients and/or in patients with other co-morbidities, the risk of hyperkalemia, which may be fatal, is increased. Monitoring of potassium should be undertaken as appropriate.

### Aortic and Mitral Valve Stenosis, Obstructive Hypertrophic Cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral valve stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

### Renal Impairment

As a consequence of inhibiting the RAS, 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 RAS (e.g., patients with severe congestive heart failure, renal artery stenosis, or volume depletion), treatment with ACE inhibitors and angiotensin II 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.

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.

Pregnancy

Category D

When pregnancy is detected, discontinue azilsartan as soon as possible. Use of drugs that affect the RAS 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. 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 RAS 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 RAS 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 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 azilsartan for hypotension, oliguria, and hyperkalemia.

Lactation

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

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

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.

Geriatric Use

No dose adjustment with azilsartan is necessary in elderly patients. Abnormally high serum creatinine values are 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 is observed.

Undesirable Effects

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 4814 patients were evaluated for safety when treated with azilsartan at doses of 20, 40, or 80 mg in clinical trials. Treatment with azilsartan was well-tolerated with an overall incidence of adverse reactions similar to placebo. The rate of withdrawals due to adverse events in placebo-controlled monotherapy and combination therapy trials was 2.4% (19/801) for placebo, 2.2% (24/1072) for azilsartan 40 mg, and 2.7% (29/1074) for azilsartan 80 mg. The most common adverse event leading to discontinuation, hypotension/orthostatic hypotension, was reported by 0.4% (8/2146) patients randomized to azilsartan 40 mg or 80 mg compared to 0% (0/801) patients randomized to placebo. Generally, adverse reactions were mild, not dose related, and similar regardless of age, gender, and race.

In placebo-controlled monotherapy trials, diarrhea was reported up to 2% in patients treated with azilsartan 80 mg daily compared with 0.5% of patients on placebo.

Other adverse reactions with a plausible relationship to treatment that have been reported with an incidence of >0.3% and greater than placebo in more than 3300 patients treated with azilsartan in controlled trials are listed below:

- **Gastrointestinal Disorders:** nausea
- **General Disorders and Administration Site Conditions:** asthenia, fatigue, peripheral edema
- **Vascular Disorders:** hypotension
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasm
- **Nervous System Disorders:** dizziness, dizziness postural
- **Respiratory, Thoracic, and Mediastinal Disorders:** cough

Clinical Laboratory Findings

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

**Serum Creatinine**

Small reversible increases in serum creatinine and serum creatinine phosphokinase are seen in patients receiving 80 mg of azilsartan. The increase may be larger when coadministered with chlorthalidone or hydrochlorothiazide.

In addition, patients taking azilsartan who had moderate to severe renal impairment at baseline or who were >75 years of age were more likely to report serum creatinine increases.

**Hemoglobin/ Hematocrit**

Low hemoglobin, hematocrit, and red blood cells counts were observed in 0.2%, 0.4%, and 0.3% of azilsartan-treated subjects, respectively. None of these abnormalities were reported in the placebo group.

Low and high markedly abnormal platelet and white blood cells counts were observed in <0.1% of subjects.

Post-marketing Experience

The following adverse reactions have been identified during the post-marketing use of azilsartan. 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.

Nausea, muscle spasms, rash, pruritus, angioedema

Safety Data from Clinical Study Done by the Manufacturer

Dizziness and headache were the most commonly reported adverse events. Dizziness was reported 4.08% patients in azilsartan 40 mg group, 3.88% in azilsartan 80 mg group and 3.92% in telmisartan 40 mg group. Headache was reported 4.08% patients in azilsartan 40 mg group, 5.83% in azilsartan 80 mg group and 4.90% in telmisartan 40 mg group. Blood creatinine increased was reported in 1 patient in all the treatment groups. Hyperkalemia was reported 2.91% patients in azilsartan 80 mg group and 1.02% in azilsartan 40 mg group. Myalgia was reported 1.96% patients in telmisartan 40 mg group, 1.02% in azilsartan 40 mg group and 0.97% in azilsartan 80 mg group.

The adverse events which are at least possibly related to azilsartan are listed below:

- Blood and lymphatic System Disorders: Eosinophilia
- Gastrointestinal disorders: Constipation, diarrhea, gastritis
- Investigations: Blood creatinine increased, blood potassium increased
- Metabolism and nutrition disorders: Hyperkalemia
- Musculoskeletal and connective tissue disorders: Myalgia, neck pain
- Nervous system disorders: Dizziness, headache
- Psychiatric disorders: Restlessness
- Respiratory and urinary disorders: Renal impairment
- Respiratory, thoracic and mediastinal disorders: Cough
- Vascular disorders: Hypotension, orthostatic hypotension

Overdosage

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness. Limited data are available related to overdosage in humans. During controlled clinical trials in healthy subjects, once-daily doses up to 320 mg of azilsartan 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.

Incompatibility

Not applicable

Shelf-Life

24 months

Storage And Handling Instructions

Store protected from moisture at a temperature not exceeding 30°C.

Keep out of reach of children.

Packaging Information

ZILANCE 40: Strip of 10 tablets
If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects you can help provide more information on the safety of this product.

ZILANCE Tablets

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