FOR THE USE OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY ONLY

MYOTAN® 40 / 80

(Azilsartan Medoxomil Tablets 40mg / 80mg)

GENERIC NAME

Azilsartan Medoxomil Tablets 40mg / 80mg

COMPOSITION

Each film coated tablet contains:

Azilsartan Kamedoxomil

equivalent to Azilsartan Medoxomil……40 mg / 80mg

Colour: Titanium Dioxide IP

DOSAGE FORM/S

Film coated tablets

INDICATION

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

DOSE 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

USE IN SPECIAL POPULATIONS (such as pregnant women, lactating women, paediatric patients, geriatric patients etc)

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 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

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. 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

CONTRA-INDICATIONS;

Do not co-administer Aliskiren with Azilsartan in patients with diabetes.

WARNINGS; 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 co-administer aliskiren with Azilsartan in patients with diabetes. Avoid use of aliskiren with Azilsartan in patients with renal impairment (GFR <60ml/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

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.

Treatment with Azilsartan was well-tolerated with an overall incidence of adverse reactions similar to placebo. The most common adverse event leading to discontinuation was hypotension/orthostatic hypotension. Generally, adverse reactions were mild, not dose related, and similar regardless of age, gender, and race.

Other adverse reactions with a plausible relationship to Azilsartan are listed below:

Gastrointestinal Disorders: nausea, Dirrhoea

General Disorders and Administration Site Conditions: asthenia, fatigue

Musculoskeletal and Connective Tissue Disorders: muscle spasm

Nervous System Disorders: dizziness, dizziness postural

Respiratory, Thoracic, and Mediastinal Disorders: cough

Clinical Laboratory Findings

Clinically relevant changes in standard laboratory parameters were uncommon with administration of Azilsartan.

Serum creatinine

Small reversible increases in serum creatinine are seen in patients receiving 80 mg of Azilsartan. The increase may be larger when co-administered 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 RBC counts were observed in Azilsartan-treated subjects. Low and high markedly abnormal platelet and WBC counts were observed in<0.1% of subjects.

Postmarketing 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

OVERDOSE

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

PHARMACODYNAMIC AND PHARMACOKINETIC 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 AT_2 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 AT_1 receptor than for the AT_2 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 reported 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_{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 and Elimination

Azilsartan is metabolized to two primary metabolites. The major metabolite in plasma is formed by Odealkylation, 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 ^{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.

INCOMPATIBILITIES

Not applicable

PACKAGING INFORMATION

10 tablets in blister, 3 such blisters in a carton

STORAGE AND HANDLING INSTRUCTIONS

Store in a dry & dark place at a temperature not exceeding 25°C.
Keep out of reach of children.

Manufactured in India by:
SYNOKEM PHARMACEUTICALS LTD.
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