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AZOR® (amlodipine and olmesartan medoxomil) Fact Sheet

- **AZOR®** (amlodipine and olmesartan medoxomil) is a two-in-one combination product indicated for the treatment of hypertension that can be used alone or with other antihypertensive agents.
    - **AZOR** can be used as initial therapy in patients who are likely to need multiple antihypertensive agents to achieve blood pressure goal.
    - Initial therapy with **AZOR** is not recommended in patients ≥75 years old or hepatically impaired patients.

- The U.S. Food and Drug Administration (FDA) granted marketing approval for **AZOR** as a second-line therapy in September 2007. Approval as an initial or first-line therapy was received in May 2009. **AZOR** is marketed by Daiichi Sankyo, Inc.

Importance of Hypertension Control

- Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions (heart attacks). These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including the class to which **AZOR** principally belongs. There are no controlled trials demonstrating risk reduction with **AZOR.**

- Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals.

Mechanism of Action

- AZOR combines the complementary actions of the dihydropyridine calcium channel blocker (CCB) amlodipine, which inhibits the entrance of calcium into the blood vessel walls and heart muscle, with olmesartan medoxomil, the active ingredient in **BENICAR®** (olmesartan medoxomil), which blocks the vasoconstrictor effects of angiotensin II receptors by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Angiotensin II is a substance found in the body that causes vasoconstriction of blood vessels leading to an increase in blood pressure. Together the two medicines allow blood vessels to relax to help reduce blood pressure.

Clinical Data

- In its pivotal registrational clinical trial, **AZOR** produced significant mean reductions in seated systolic and diastolic blood pressure in patients with hypertension. In this study, **AZOR** 10/40 mg reduced systolic blood pressure by an average of 30.1 mm Hg and the diastolic reading by an average of 19.0 mm Hg. These results were in comparison with mean reductions of 19.7/12.7 mm Hg for amlodipine 10 mg and 16.1/10.2 mm Hg for olmesartan medoxomil 40 mg alone (placebo= 4.8/3.1 mm Hg). When compared to amlodipine 10 mg alone, **AZOR** 10/40 mg resulted in a 53 percent greater reduction in the mean change of systolic blood pressure. The mean blood pressure at baseline was 164/102 mm Hg for the overall population.[1]

- An analysis of patient subgroups from the pivotal registrational trial demonstrated the efficacy of **AZOR** in several key difficult to treat patient groups including:
  - 29/16 mm Hg mean reduction from baseline in Black patients (placebo 4/1 mm Hg)
  - 30/18 mm Hg mean reduction from baseline in obese patients (BMI at or over 30 kg/m^2) (placebo 5/3 mm Hg)
  - 30/18 mm Hg mean reduction from baseline in diabetes patients (placebo 15/8 mm Hg)

- The placebo-subtracted incidence for **AZOR** was 5.7 percent (5/20 mg), 6.2 percent (5/40 mg), 13.3 percent (10/20 mg), and 11.2 percent (10/40 mg). The edema incidence for placebo was 12.3 percent.

  - Adverse reactions seen at lower rates but at about the same or greater incidence as in patients receiving placebo included hypotension, orthostatic hypotension, rash, pruritus, palpitation, urinary frequency, and nocturia.
  - In individual clinical trials of amlodipine and olmesartan medoxomil, other commonly reported adverse reactions included headache, dizziness, palpitation, somnolence, and flushing.

Dose Strengths

- There are currently four approved doses of **AZOR**:
  - 5 mg amlodipine/20 mg olmesartan medoxomil
  - 5 mg amlodipine/40 mg olmesartan medoxomil
  - 10 mg amlodipine/20 mg olmesartan medoxomil
  - 10 mg amlodipine/40 mg olmesartan medoxomil

- Maximum antihypertensive effects are attained within 2 weeks after a change in dose. The maximum recommended dose of **AZOR** is 10/40 mg. For initial therapy, the usual starting dose of **AZOR** is 5/20 mg once daily.

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Important Safety Information for AZOR®

WARNING: FETAL TOXICITY
- **When pregnancy is detected, discontinue AZOR as soon as possible**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See WARNINGS AND PRECAUTIONS: Fetal Toxicity**

CONTRAINDICATION

Do not co-administer aliskiren with AZOR in patients with diabetes.

WARNINGS AND PRECAUTIONS

Fetal Toxicity: AZOR is **Pregnancy Category D**.

Hypotension in Volume- or Salt-Depleted Patients: In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with AZOR.

Impaired Renal Function: Monitor for worsening renal function in patients with renal impairment while on AZOR.

In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (eg, patients with severe congestive heart failure), treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists 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 AZOR.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported, and similar results may be expected with AZOR.

Sprue-like Enteropathy: Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, exclude other etiologies. Consider discontinuation of AZOR in cases where no other etiology is identified.

Hepatic Impairment: Initial therapy with AZOR is not recommended in hepatically impaired patients. In patients with severe hepatic impairment, exercise caution with AZOR.

Vasodilation: Although vasodilation attributable to amlodipine (a component in AZOR) is gradual in onset, acute hypotension has rarely been reported after oral administration. Patients with severe aortic stenosis may be at particular risk.

Increased Angina and/or Myocardial Infarction: Patients taking AZOR, particularly those with severe obstructive coronary artery disease, may develop increased frequency, duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dose increase.

Laboratory Tests: There was a greater decrease in hemoglobin and hematocrit with AZOR compared to either component alone. Other lab abnormalities may include increased blood creatinine levels and hyperkalemia (olmesartan medoxomil) and hepatic enzyme elevations (amlodipine).

DRUG INTERACTIONS

Non-Steroidal Anti-Inflammatory Agents: Concurrent administration of non-steroidal anti-inflammatory drugs (NSAIDs) may lead to increased risk of renal impairment (including possible acute renal failure) and loss of antihypertensive effect of AZOR.

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 AZOR and other agents that affect the RAS.

Avoid use of aliskiren with AZOR in patients with renal impairment (GFR <60 mL/min).

Concurrent Use with Colesevelam Hydrochloride: Concurrent administration of colesevelam hydrochloride with AZOR reduces the systemic exposure and peak plasma concentration of olmesartan. Consider administering olmesartan at least 4 hours before the colesevelam hydrochloride dose.

Effect of Amlodipine on Simvastatin: Due to increased exposure to simvastatin, when co-administered with amlodipine (a component in AZOR), do not exceed doses of greater than 20 mg daily of simvastatin.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including AZOR. Monitor serum lithium levels during concomitant use.

ADVERSE REACTIONS

The most common adverse reaction (incidence ≥3%) in patients treated with AZOR was edema.

USE IN SPECIFIC PATIENT POPULATIONS

Nursing Mothers: Avoid use while nursing; discontinue either nursing or the drug.

Please see Full Prescribing Information for AZOR.

Reference:
[1] Chrysant SG, Melino M, Karki S, Lee J, Heyrman R. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther*. 2008;30:587-604.