Azilsartan Medoxomil (Edarbi)
The Eighth Angiotensin II Receptor Blocker

Jocelyn D. Jones, PharmD, BCPS; Sylvia H. Jackson, PharmD, MEd, CDE; Carmen Agboton, PharmD; and Tonya S. Martin, PharmD, CGP, MAEd

INTRODUCTION
Hypertension affects approximately one in three adults in the U.S. and is a major risk factor for cardiovascular disease. Each year, hypertension contributes to one of every seven deaths in the U.S. and to nearly half of all cardiovascular disease-related deaths, including stroke. If all hypertensive patients were treated effectively to reach the blood pressure (BP) goals established in current clinical guidelines, 46,000 deaths might be averted each year. In addition to the cost in lives lost, hypertension is costly to the health care system in terms of dollars spent. The American Heart Association recently estimated that the direct and indirect costs of hypertension total more than $93.5 billion per year and that cardiovascular disease and stroke account for 17% of total annual health expenditures in the U.S.

Eight classes of medications are currently used in the treatment of hypertension. They include diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-adrenergic blockers, alpha-adrenergic blockers, calcium-channel blockers (CCBs), central alpha-adrenergic receptor agonists (also called central adrenergic inhibitors), and direct renin inhibitors (DRIs). Until recently, the ARB class consisted of seven agents: candesartan (Atacand, AstraZeneca), eprosartan (Teveten, Abbott), irbesartan (Avapro, Bristol-Myers Squibb/Sanofi), losartan (Cozaar, Merck), olmesartan (Benicar, Daiichi Sankyo), telmisartan (Micardis, Boehringer Ingelheim), and valsartan ( Diovan, Novartis). Many of these drugs are available in combination with other antihypertensive agents, such as the DRI aliskiren (Tekturna, Novartis), the CCB amlodipine (Norvasc, Pfizer), and the thiazide diuretic hydrochlorothiazide (HCTZ).

Four ARBs have been approved for indications other than hypertension. Candesartan and valsartan may be used for the treatment of heart failure, and irbesartan and losartan are indicated for the treatment of nephropathy in patients with type-2 diabetes and hypertension.

Azilsartan medoxomil (Edarbi, Takeda) is a new addition to the ARB class of antihypertensive agents. It received FDA approval in February 2011.

INDICATION AND USAGE
Azilsartan medoxomil is indicated for the treatment of hypertension in adults 18 years of age and older. It is approved for use alone or in combination with other antihypertensive drugs.

CHEMICAL STRUCTURE AND PHYSICAL PROPERTIES
Figure 1 shows the chemical structure of azilsartan kamedoxomil, the potassium salt of azilsartan medoxomil. This salt is practically insoluble in water and is freely soluble in methanol. Each white, round, unscored tablet of azilsartan medoxomil contains 42.68 mg or 85.36 mg of the potassium salt, which is equivalent to 40 mg and 80 mg of azilsartan medoxomil, respectively.

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**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Angiotensin II, a peptide hormone, is the principal pressor agent in the renin-angiotensin system (RAS). Angiotensin II is a potent, direct vasoconstrictor. It stimulates the synthesis and release of aldosterone and also promotes renal tubular reabsorption of sodium, resulting in water retention.

As an ARB, azilsartan medoxomil selectively inhibits angiotensin II from binding to the angiotensin II type-1 receptor (AT1). This receptor inhibition provides the antihypertensive activity of azilsartan medoxomil because it blocks the pressor effects of angiotensin II.

**Pharmacodynamics**

The antihypertensive effects of azilsartan medoxomil are dose-related. This characteristic was observed after an infusion of angiotensin II in healthy subjects. A 32-mg dose of azilsartan medoxomil decreased the maximal pressor effect of angiotensin II by approximately 90% when the drug reached peak plasma concentration. Twenty-four hours after administration, azilsartan medoxomil lowered the pressor effect by approximately 60%.

In healthy subjects, single and repeated doses of azilsartan medoxomil increased the plasma concentrations of both angiotensin I and angiotensin II. Renin activity also increased, whereas plasma aldosterone levels decreased.

**Pharmacokinetics**

Absorption and Distribution. Azilsartan medoxomil is a prodrug. It is hydrolyzed to the active moiety, azilsartan, in the gastrointestinal (GI) tract during the absorption phase. The estimated absolute bioavailability of azilsartan is 60%. Absorption is not affected by food, and peak plasma concentrations are reached within 1.5 to 3 hours.

The apparent volume of distribution of azilsartan medoxomil is 16 L. Similar to other ARBs, the drug is highly bound to plasma proteins (99%). When azilsartan was studied in rats, a minimal amount of radioactivity was found to have crossed the blood–brain barrier. In addition, azilsartan crossed the placental barrier and was distributed to the fetus.

Metabolism and Elimination. The enzyme principally responsible for the metabolism of azilsartan is cytochrome P450 (CYP) 2C9. Azilsartan is metabolized to two primary metabolites, M-I and M-II, by decarboxylation and O-dealkylation, respectively. These metabolites have low affinity for the AT1 receptor and therefore have no effect on the pharmacologic activity of azilsartan medoxomil.

Renal clearance of this medication is estimated to be 2.3 mL/minute. The elimination half-life is 11 hours, and steady-state concentrations are reached within 5 days. Fifty-five percent of the product is eliminated in the feces, and 42% is excreted in the urine, with 15% of the drug unchanged.

**PIVOTAL CLINICAL TRIALS**

The FDA’s approval of azilsartan medoxomil was based on the results of seven double-blind, randomized studies involving a total of 5,941 patients with hypertension. The studies ranged from 6 weeks to 6 months in duration, and the doses of azilsartan medoxomil ranged from 20 mg to 80 mg. Pivotal clinical trials of azilsartan medoxomil are described next.

**White et al.**

White and colleagues conducted a 6-week, randomized, double-blind, multicenter, placebo-controlled and active-controlled study to compare the antihypertensive effects of the two available doses of azilsartan medoxomil (40 and 80 mg) with that of valsartan (320 mg) and olmesartan medoxomil (40 mg).

The study included men and women 18 years of age and older whose clinic systolic BP was between 150 and 180 mm Hg, and whose 24-hour mean systolic BP was between 150 and 180 mm Hg. Patients were excluded from the study if they had secondary hypertension; severe diastolic hypertension; significant renal, metabolic, or psychiatric disorders; unstable cardiovascular disease, or type-1 or poorly controlled type-2 diabetes mellitus. Night-shift workers, pregnant women, and nursing mothers were also excluded.

Eligible patients underwent a 3- to 4-week washout period, which was concurrent with a 2-week, single-blind, placebo-administration period. The patients were then randomly assigned to receive daily doses of azilsartan medoxomil 20 mg, azilsartan medoxomil 40 mg, valsartan 160 mg, olmesartan 20 mg, or placebo. Two weeks later, the doses were doubled in each treatment group, and these higher doses were continued for an additional 4 weeks.

A total of 1,291 patients were randomly assigned to the five treatment groups. The patients’ mean age was 56 years, and 54% were men. The primary efficacy endpoint was the change from baseline in the 24-hour mean systolic BP after 6 weeks of treatment. BP measurements were assessed in the clinic at baseline and at 2, 4, and 6 weeks after randomization. The study also included ambulatory BP monitoring (ABPM). The ABPM recordings were assessed at baseline and at 6 weeks after randomization.

Data from 1,088 evaluable patients were analyzed to determine non-inferiority and superiority of the two doses of azilsartan medoxomil compared with valsartan and olmesartan. Table 1 lists the changes in systolic BP observed in each treatment group. The study results showed that azilsartan medoxomil 80 mg was more effective than maximal doses of valsartan and olmesartan in reducing systolic BP without increasing the incidence of adverse events (AEs).

**Bönnner et al.**

A 24-week, randomized, double-blind study was conducted to compare the antihypertensive efficacy and safety of azilsartan medoxomil with that of the ACE inhibitor ramipril (Altace, Monarch). Patients with clinic systolic BPs ranging from 150 to 180 mm Hg were included in the study.

The patients were randomly assigned to receive daily doses of azilsartan medoxomil 20 mg, azilsartan medoxomil 40 mg, or ramipril 10 mg. For the first 2 weeks, the patients received lower initial doses of the study drugs (i.e., azilsartan medoxomil 20 mg and ramipril 2.5 mg). The doses were then maximized in each treatment group for the remainder of the study.

A total of 884 men and women were treated. The patients’ mean age was 57 years, and 52.4% were men. The primary efficacy endpoint was the change in trough sitting clinic systolic BP from baseline. Secondary endpoints included response rates (i.e., clinic systolic BP and diastolic BP below 140/90 mm Hg and/or a reduction of 20/10 mm Hg or
Azilsartan medoxomil 40 and 80 mg reduced both clinic and mean 24-hour systolic BP significantly more than did ramipril 10 mg (Table 2). Response rates were also significantly greater with azilsartan medoxomil 40 and 80 mg (54.0% and 53.6%, respectively) than with ramipril 10 mg (33.8%; P < 0.001). In addition, AEs leading to discontinuation of treatment (2.4% and 3.1% vs. 4.8%) and cough (1.0% and 1.4% vs. 8.2%) were less frequent with both doses of azilsartan compared with ramipril.

The investigators concluded that long-term treatment with azilsartan medoxomil was more effective than long-term ramipril in reducing BP and that azilsartan medoxomil was well tolerated in patients with hypertension.

**Table 1 Changes From Baseline in 24-hour Ambulatory Systolic Blood Pressure (mm Hg)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 134)</th>
<th>Azilsartan Medoxomil 40 mg (n = 237)</th>
<th>Azilsartan Medoxomil 80 mg (n = 229)</th>
<th>Valsartan 320 mg (n = 234)</th>
<th>Olmesartan 40 mg (n = 254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 24-hour systolic BP, mean (SE)</td>
<td>144.3 (0.9)</td>
<td>144.4 (0.6)</td>
<td>144.6 (0.7)</td>
<td>146.3 (0.6)</td>
<td>144.4 (0.6)</td>
</tr>
<tr>
<td>Change in 24-hour systolic BP (SE)</td>
<td>−0.3 ± 0.9</td>
<td>−13.4 ± 0.7</td>
<td>−14.5 ± 0.7</td>
<td>−10.2 ± 0.7</td>
<td>−12.0 ± 0.7</td>
</tr>
<tr>
<td>Azilsartan vs. valsartan:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>−3.2 (−5.1/−1.3)</td>
<td>−4.3 (−6.3/−2.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azilsartan vs. olmesartan:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>−1.4 (−3.3/0.5) = 0.14</td>
<td>−2.5 (−4.4/−0.6) = 0.009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.136</td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Sica et al. Thiazide diuretics are common adjuncts to antihypertensive therapy with ARBs and ACE inhibitors. Most clinical trials involving thiazide diuretic regimens have evaluated the long-acting, thiazide-like diuretic chlorothalidone (Thalitone, Monarch). However, none of the currently available fixed-dose ARB combinations of azilsartan medoxomil 40 or 80 mg with amldopine 5 mg could be efficacious in the treatment of patients with stage 2 hypertension. Moreover, the addition of amldopine may help to reduce the occurrence of peripheral edema associated with azilsartan medoxomil.

**Table 2 Changes From Baseline in Clinic Systolic Blood Pressure (mm Hg)**

<table>
<thead>
<tr>
<th></th>
<th>Azilsartan Medoxomil 40 mg (n = 294)</th>
<th>Azilsartan Medoxomil 80 mg (n = 293)</th>
<th>Ramipril 10 mg (n = 292)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline systolic BP, mean</td>
<td>160.9 ± 0.5</td>
<td>161.5 ± 0.5</td>
<td>161.4 ± 0.5</td>
</tr>
<tr>
<td>Change in week 24, systolic BP</td>
<td>−20.6 ± 0.9</td>
<td>−21.2 ± 0.9</td>
<td>−12.2 ± 0.9</td>
</tr>
<tr>
<td>Change vs. ramipril: difference (95% CI) P value</td>
<td>−8.4 (−11.0/−5.8) &lt; 0.001</td>
<td>−9.0 (−11.7/−6.4) &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

combination products contains that diuretic agent. Sica and colleagues therefore conducted a 6-week randomized, double-blind, placebo-controlled trial to evaluate the efficacy of azilsartan medoxomil combined with chlorthalidone in patients with stage 2 hypertension.

Individuals were included in the study if they had a clinic systolic BP of 160 to 190 mm Hg and a 24-hour mean systolic BP of 140 to 180 mm Hg. Approximately 450 patients were randomly assigned to receive azilsartan medoxomil 40 mg, azilsartan medoxomil 80 mg, or placebo, each administered with chlorthalidone 25 mg. The primary endpoint was the change from baseline in 24-hour mean systolic BP.

Absolute reductions in 24-hour mean systolic BP were greater in the groups overall compared with the group given chlorthalidone and placebo (−15.9 mm Hg; −31.3 mm Hg, respectively) compared with the group given azilsartan medoxomil and chlorthalidone.15 Fifteen percent more patients in the HCTZ group required an increase in the diuretic dose compared with the chlorthalidone group.

The primary endpoint was the change in clinic systolic BP from baseline. Ten weeks after the start of the study, the reduction in clinic systolic BP was greater in the group receiving azilsartan medoxomil and chlorthalidone compared with the group given azilsartan medoxomil and HCTZ (−37.8 mm Hg vs. −32.8 mm Hg, respectively; \( P < 0.001 \)). The fixed-dose combination of azilsartan medoxomil and chlorthalidone significantly decreased clinic BP measurements and 24-hour mean systolic BP more than azilsartan medoxomil and HCTZ.

Conflicting study data have been published regarding the relative efficacy and dose equivalence of the various diuretic agents. No fixed-dose combinations of an ARB and chlorthalidone are currently available in the U.S. A New Drug Application (NDA) has been submitted to the FDA for approval of a fixed-dose product consisting of azilsartan medoxomil and chlorthalidone.16

The most common AEs (with an incidence of 2% or greater) occurring in hypertensive patients treated with the recommended doses of azilsartan medoxomil plus chlorthalidone included increased levels of creatinine (11.0%), dizziness (8.2%), increased uric acid levels (3.8%), elevated blood urea nitrogen (2.8%), and fatigue (2.5%). Most creatinine elevations were transient and were generally associated with large reductions in BP.

**ADVERSE DRUG EFFECTS**

In clinical trials, 4,814 patients were evaluated for safety during azilsartan medoxomil therapy at daily doses of 20, 40, and 80 mg. A total of 1,704 patients were treated for at least 6 months, including 588 who were treated for at least 1 year. Azilsartan medoxomil was well tolerated, and the incidence of AEs was similar to that of placebo.

Rates of withdrawals resulting from AEs were 2.4% for placebo, 2.2% for azilsartan medoxomil 40 mg, and 2.7% for azilsartan medoxomil 80 mg. Hypotension and orthostatic hypotension were the most common AEs leading to discontinuation of therapy. Both AEs

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**Table 3 Changes in Systolic and Diastolic Blood Pressures (mm Hg)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 185)</th>
<th>Azilsartan Medoxomil 40 mg (n = 189)</th>
<th>Azilsartan Medoxomil 80 mg (n = 188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour mean ABPM, No. patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline systolic BP/diastolic BP</td>
<td>166 (90)</td>
<td>165 (87)</td>
<td>166 (88)</td>
</tr>
<tr>
<td>Change</td>
<td>–13.6/–7.8</td>
<td>–24.8/–15.3</td>
<td>–24.5/–15.4</td>
</tr>
<tr>
<td>Change vs. placebo (95% CI)</td>
<td>–12.5/–7.7</td>
<td>–13.3/–9.1/–8.8/–6.1</td>
<td>–9.0/–6.3</td>
</tr>
<tr>
<td>Clinic, No. patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline systolic BP/diastolic BP</td>
<td>179 (97)</td>
<td>187 (99)</td>
<td>183 (97)</td>
</tr>
<tr>
<td>Change</td>
<td>–15.9/–7.1</td>
<td>–27.0/–12.0</td>
<td>–25.5/–12.7</td>
</tr>
<tr>
<td>Change vs. placebo (95% CI)</td>
<td>–11.0/–4.9</td>
<td>–13.9/–8.1/–6.6</td>
<td>–7.3/–3.9</td>
</tr>
</tbody>
</table>

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CI = confidence interval.

* \( P < 0.001 \) vs. amlodipine + placebo.

occurred in 0.4% of the patients treated with azilsartan medoxomil compared with 0% of the patients receiving placebo. Most of the changes in standard laboratory parameters were not clinically relevant. A small, reversible increase in serum creatinine was observed with patients receiving azilsartan medoxomil 80 mg. This increase may be larger when azilsartan medoxomil is coadministered with chlorothalidone or HCTZ. In addition, serum creatinine levels may be increased in patients with moderate or severe renal impairment or in those who are 75 years of age or older.

Diarrhea was the most common AE associated with azilsartan medoxomil, occurring in up to 2% of patients receiving the 80-mg dose in placebo-controlled monotherapy trials, compared with 0.5% of patients who received placebo. Other AEs with a plausible relationship to treatment with azilsartan medoxomil included nausea, asthenia, fatigue, muscle spasm, dizziness, and cough. Low hemoglobin, hematocrit, and red blood cell counts were observed in 0.2%, 0.4%, and 0.3% of patients receiving azilsartan medoxomil, respectively.

DRUG INTERACTIONS

Because azilsartan medoxomil is metabolized by CYP2C9, caution is advised when azilsartan is administered with strong modulators of this enzyme. Other antihypertensive agents should also be used with caution in combination with azilsartan medoxomil. Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors, may inhibit renal function when administered with ARBs. This effect is reversible and is most likely to occur in elderly, volume-depleted, or renally compromised patients.

Renal function should be monitored periodically in these patients when azilsartan medoxomil is used with NSAIDs.

CONTRAINDICATIONS

There are no clinical contraindications to the use of azilsartan medoxomil.

WARNINGS

The labeling for azilsartan medoxomil includes a boxed warning regarding the use of this drug in pregnancy. When pregnancy is detected, azilsartan medoxomil should be discontinued as soon as possible. Drugs that act on the RAS, such as azilsartan medoxomil, can cause injury and death to the developing fetus. No clinical studies of azilsartan medoxomil have been conducted in pregnant women. Azilsartan medoxomil is a Pregnancy Category C drug during the first trimester and a Pregnancy Category D drug during the second and third trimesters. It is not known whether this medication is excreted in human milk. Low concentrations of the drug have been found in the milk of lactating rats.

The RAS is activated in patients who are volume-depleted or salt-depleted, including patients taking high doses of diuretics. The use of azilsartan medoxomil may result in symptomatic hypotension in that population. Volume and salt depletion must be corrected before initiation of azilsartan medoxomil, and treatment should be started with a daily dose of 40 mg.

A transient hypotensive episode does not constitute a contraindication to the use of azilsartan medoxomil. The drug may be continued when the patient’s BP has been stabilized.

Changes in renal function may be anticipated when patients are taking medications that inhibit the RAS. Azilsartan medoxomil, like other ARBs, may cause oliguria or progressive azotemia in volume-depleted patients, in patients with severe congestive heart failure, and in patients with renal stenosis.

DOSE AND ADMINISTRATION

In adults, the recommended dosage of azilsartan medoxomil is 80 mg taken orally once daily with or without food. A starting dose of 40 mg should be considered in patients receiving high doses of diuretics and in volume-depleted and salt-depleted patients.

Azilsartan medoxomil may be used with other antihypertensive agents. It has not been studied in patients younger than 18 years of age. Dose adjustments are unnecessary in elderly patients, in those with renal impairment, or in those with mild-to-moderate hepatic dysfunction. The drug’s safety and efficacy have not been established in patients with severe hepatic impairment.

COST

The average wholesale price (AWP) for a month’s supply of azilsartan medoxomil 40 or 80 mg is approximately $90.

P&T COMMITTEE CONSIDERATIONS

ARBs are not considered to be first-line agents for the treatment of hypertension. These medications are often used to treat hypertensive patients who are intolerant of ACE inhibitors.

In a pivotal clinical study, azilsartan medoxomil 80 mg proved to be significantly more effective at lowering systolic BP than either valsartan 320 mg or olmesartan 40 mg in patients with stage 1 or stage 2 hypertension. The placebo-adjusted 24-hour systolic BP was reduced by 14.3 mm Hg compared with reductions of 10.0 mm Hg with valsartan (P < 0.001) and by 11.7 mm Hg with olmesartan (P = 0.009). In addition, as part of a recently published study in which systolic BP was measured over 24 hours in patients with primary hypertension, azilsartan medoxomil 80 mg was significantly more effective at lowering systolic BP compared with valsartan 320 mg (–15.3 vs. –11.3 mm Hg, respectively; P < 0.001).

In another study of patients with primary hypertension, azilsartan medoxomil 80 mg lowered systolic BP by 14.6 mm Hg compared with a reduction of 12.6 mm Hg with olmesartan 40 mg (P = 0.038).

A month’s supply of the maximum strength of azilsartan medoxomil 80 mg costs less than other currently available ARBs (approximately $90 wholesale vs. $113 to $134, respectively), making it one of the most cost-effective drugs in its class.

Azilsartan medoxomil may also become the first ARB to be combined with the potent, long-acting thiazide-like diuretic chlorothalidone. This combination would be an attractive option for patients who require more aggressive lowering of systolic BP.

CONCLUSION

Azilsartan medoxomil is the eighth ARB to be approved for the treatment of hypertension. Recent studies have demonstrated that azilsartan is more effective than the ARBs olmesartan and valsartan and the ACE inhibitor ramipril at lowering systolic BP. A recent study also
showed that the combination of azilsartan medoxomil and the calcium-channel blocker amlopidine is effective at lowering systolic BP, with a reduced incidence of peripheral edema.12

Moreover, azilsartan medoxomil, in combination with the thiazide-like diuretic chlorthalidone, was more effective in lowering systolic BP than azilsartan plus HCTZ.14 Many experts have expressed concern with the implication of azilsartan’s superiority, given that the comparison includes chlorthalidone, a diuretic with potency greater than that of HCTZ. Nevertheless, combining an ARB with chlorthalidone may be expected to decrease the pill burden, increase adherence, and provide practitioners with another viable option for treating patients with hypertension.

REFERENCES


4. Atacand (candesartan cilexetil), prescribing information. Wilmington, Del.: AstraZeneca; April 2011.


