Formulary Forum

Azilsartan Medoxomil: A New Angiotensin II Receptor Antagonist for Treatment of Hypertension

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OBJECTIVE: To evaluate the efficacy, safety, and clinical role of azilsartan medoxomil, an angiotensin II receptor blocker (ARB) that recently gained Food and Drug Administration approval for lowering of blood pressure (BP) in patients with hypertension.

DATA SOURCES: A systematic review of the literature was performed through August 2011 using MEDLINE, Web of Science, and *International Pharmaceutical Abstracts* and the key words and MeSH terms azilsartan, azilsartan medoxomil, TAK-491, TAK-536, and Edarbi. Abstracts presented in the last 2 years from the annual meetings of appropriate medical societies were reviewed in addition to a search of clinicaltrials.gov.

STUDY SELECTION AND DATA EXTRACTION: Studies eligible for inclusion were in vitro or in vivo evaluations of azilsartan medoxomil, with no restrictions on patient population or indication. Data related to the patient populations and outcomes of interest were extracted from each publication.

DATA SYNTHESIS: Three trials are available in full publication form with others available only as abstracts. Azilsartan medoxomil 40 mg and 80 mg daily significantly improves both systolic and diastolic BP from baseline compared with placebo, and the 80-mg dose has greater efficacy than other ARBs, including olmesartan 40 mg daily and valsartan 320 mg daily. Improvements in both 24-hour BP using ambulatory monitoring and clinic monitoring have been seen with azilsartan medoxomil as well as a higher proportion of patients reaching the goal level. Additional information shows added BP lowering when azilsartan medoxomil is combined with chlorthalidone. Adverse events are similar with azilsartan medoxomil versus other ARBs and include headache, dizziness, urinary tract infections, and fatigue.

CONCLUSIONS: Azilsartan medoxomil is a safe and effective ARB with a unique pharmacologic profile versus other agents, including slowed angiotensin II type 1 receptor dissociation rates and improved receptor specificity. Studies have shown azilsartan medoxomil 80 mg once daily to reduce BP to a greater extent than valsartan and olmesartan, with similar safety and tolerability.

KEY WORDS: angiotensin receptor blocker, azilsartan medoxomil, blood pressure, hypertension, TAK-491.

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Pharmacologic agents that attenuate the actions of the renin-angiotensin-aldosterone system are one of the most popular antihypertensive strategies for patients with elevated blood pressure (BP).[1,2] This includes the angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), direct renin inhibitors, and aldosterone antagonists. The ARBs inhibit the action of angiotensin II (AT-II) by binding to and inhibiting the AT-II type 1 (AT_1) receptor. This induces a dose-dependent decrease in peripheral resistance, reduction in vascular smooth muscle contraction, and reduced synthesis and effects of aldosterone on the kidneys.[3] These pharmacologic properties have led to improved outcomes with ARB use across a number of disease states, including coronary heart disease, concomitant diabetes and kidney disease, and heart failure.[4,5]

Currently, 8 ARBs have been approved for use by the Food and Drug Administration (FDA) to treat hypertension. These agents differ in their pharmacologic properties and impact on BP in both healthy and hypertensive populations.[6] This includes differences in affinity for the AT_1 receptor, duration of AT_1 antagonism, and surmountable versus in-

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surmountable antagonism.[7-9] Azilsartan medoxomil (Edarbi, Takeda Pharmaceuticals America, Inc.; Deerfield, IL) is a highly selective ARB and was approved by the FDA in February 2011 for the treatment of hypertension in adults.[10] Given the large number of ARBs that are available in the US, it is important to understand the pharmacologic and clinical characteristics of azilsartan medoxomil that may differentiate the drug from the others for hypertension management.

Data Selection

A systematic review of the literature for all relevant articles was performed through August 2011 using MEDLINE (beginning January 1950), Web of Science (v4.10), and *International Pharmaceutical Abstracts* (beginning 1977). The search strategy was developed using the key words and MeSH terms azilsartan, azilsartan medoxomil, TAK-491, TAK-536, and Edarbi. Articles were limited to those published in the English language. A manual search of references from reports of clinical trials or review articles was performed to identify additional relevant studies. Studies were eligible for inclusion if they were in vitro or in vivo evaluations of azilsartan medoxomil, with no restrictions on patient population or indication used. Product monographs were retrieved from government Web sites (http://www.fda.gov) and from the product sponsor (Takeda Pharmaceuticals). Abstracts presented in the last 2 years from the annual meeting of appropriate medical societies, including the American College of Cardiology, American Heart Association, American Society of Hypertension, European Society of Hypertension, and International Society of Hypertension were also reviewed. A search of ClinicalTrials.gov (http://www.clinicaltrials.gov) was also conducted to identify additional recently completed or ongoing studies of relevance.

Chemistry and Pharmacology

Azilsartan medoxomil is a prodrug with a molecular weight of 606.62 that is hydrolyzed within the gastrointestinal tract to azilsartan prior to absorption.[11] It is structurally related to candesartan with the exception that azilsartan medoxomil contains a 5-oxo-1,2,4-oxadiazole moiety in place of the tetrazole ring.[11] This chemical alteration has also been reported to increase the lipophilicity of azilsartan medoxomil and potentially improve its oral bioavailability.[11]

In vitro and in vivo studies have demonstrated azilsartan medoxomil to be an insurmountable selective AT_1 antagonist with greater potency and a longer-lasting pharmacologic effect compared with other ARBs. Ojima and colleagues conducted a series of pharmacologic studies in an animal model to investigate the AT_1-antagonist properties of azilsartan medoxomil compared with other currently available ARBs.[12] Azilsartan medoxomil was shown to bind to the AT_1 receptor in a concentration dependent manner with high affinity, as measured by a 50% inhibitory concentration (IC_{50}) of 2.6 nM, as compared with the ARBs olmesartan, telmisartan, valsartan, and irbesartan (IC_{50} 6.7, 5.1, 44.9, and 15.8 nM, respectively). After a washout period, azilsartan medoxomil maintained its potent inhibitory effect (IC_{50} 7.4) in contrast to the other ARBs whose effects were significantly attenuated (IC_{50} 242.5, 191.6, >10,000, and >10,000 nM, respectively). These findings suggest that azilsartan medoxomil is more potent and with more slowly dissociating AT_1 antagonist properties compared to other agents in the ARB class.[12]

A variety of potential pleiotropic effects with azilsartan medoxomil have been demonstrated, potentially supporting its investigation for treating concomitant disorders in patients with hypertension. A type 2 diabetic KK-A^y mouse model showed that both azilsartan and candesartan produced dose-dependent suppression of increases in plasma glucose levels following an oral glucose tolerance test while improving insulin sensitivity and not changing insulin concentrations.[13] Azilsartan medoxomil also significantly decreased epididymal adipose-tissue weight to a greater degree than candesartan ($p < 0.05$) (which had no significant effect versus controls). An obese Koletsky rat model study confirmed that the insulin-sensitizing effects of azilsartan were independent of changes in food intake and body weight.[14] Suppression of plasminogen activator inhibitor type-1 in the plasma, left ventricular tissues, and aortas of knockout mice was also shown in a dose-dependent manner with azilsartan medoxomil, suggesting a potential modifying effect of atherosclerotic plaque development.[15] Moreover, a dose-dependent reduction in myocardial infarction size (measured as percentage of the left ventricle) was seen in a rat model both with azilsartan medoxomil alone and in combination with pioglitazone; the latter combination also resulted in an additive effect.[16]

Pharmacokinetics

Minimal published data exist on the pharmacokinetic properties of azilsartan medoxomil. Much of the information comes from the manufacturer's prescribing information[11] and an abstract (Table 1).[17] Azilsartan medoxomil is metabolized, primarily by the CYP2C9 enzyme, to azilsartan. This is then further metabolized to the inactive M-II, which is formed via *O*-dealkylation, and the minor metabolite (M-I), which is formed through decarboxylation. The terminal half-life of azilsartan is approximately 11 hours, with an estimated renal clearance of 2.3 mL/min. No accumulation of the drug has been demonstrated following continuous once-daily dosing. Additionally, azilsartan medoxomil does not appear to have any clinically significant drug interactions. However, the prescribing information cautions about concomitant use with nonsteroidal antiinflam-

matory drugs (NSAIDs) (including cyclooxygenase-2 inhibitors), particularly in patients who are elderly or volume depleted, because of an increased risk for deterioration of renal function.[11] In addition, NSAIDs may attenuate the BP-lowering effects of azilsartan medoxomil (and all blockers of the renin-angiotensin system) and should be avoided if possible.

Clinical Trials

Three large clinical trials of azilsartan medoxomil for treating patients with various stages of hypertension are available in full publication form (Table 2).[18-20] Several other studies have been presented at conferences and are available in abstract form (Table 3).[21-25]

Table 1. Pharmacokinetics of Azilsartan[11]

Absorption	
time to maximum concentration	2.6 hours
absolute bioavailability	60%
maximum concentration	1.5-3 hours
Distribution	
volume of distribution	16 L
plasma protein binding	>99%
Metabolism	
	O-dealkylation (major metabolite) and decarboxylation (minor metabolite)
major cytochrome P450 enzyme	CYP2C9
Excretion	
clearance	2.3 mL/min
half-life	11 hours
elimination routes	Feces 55%, urine 42%

FULL-TEXT PUBLICATION STUDIES

Bakris and colleagues randomized 1275 patients (mean age 58 ± 11 years) with a diagnosis of primary hypertension to receive azilsartan medoxomil, olmesartan, or placebo for 6 weeks following a 3- to 4-week washout period (duration based on prior use of antihypertensives).[18] Each of the azilsartan medoxomil doses, as well as olmesartan, significantly reduced 24-hour systolic BP (SBP) compared with placebo ($p < 0.001$ for all doses) (Figure 1). Compared with olmesartan 40 mg, azilsartan medoxomil 40 mg was noninferior, whereas the azilsartan medoxomil 80-mg dose produced significant reductions in both 24-hour mean SBP and trough sitting clinic SBP from baseline ($p < 0.001$ for both). Results similar to those of the primary analysis were seen for both 24-hour mean diastolic BP (DBP) and clinic DBP for each comparison. These results were consistent among a variety of subgroups, based on age, sex, baseline 24-hour mean SBP, and renal function, although an attenuation of effect was seen among black versus non-black patients. The authors noted a moderately decreased effect among the black cohort of patients compared with the non-blacks; more-specific data were not available. The proportions of patients deemed responders in the azilsartan medoxomil 20-mg (48%), 40-mg (50%), and 80-mg (57%) groups were similar to those who received olmesartan 40 mg (53%) (OR 1.15; 95% CI 0.83 to 1.62; $p = 0.402$ vs azilsartan medoxomil 80 mg). Statistical comparisons between the olmesartan group and azilsartan medoxomil

Table 2. Azilsartan Medoxomil Clinical Trials Available in Full Publication

Reference	Design	Pts. (N)	Inclusion Criteria	Dosage	Duration	Primary Outcome	Results
Bakris (2011)[18]	R, DB, PC, parallel	1275	Clinic SBP 150-180 mm Hg or 24-hour mean SBP 130-170 mm Hg	AZL 20, 40, 80 mg once daily vs OLM 40 mg once daily vs Placebo	6 weeks	Change in 24-hour mean SBP by ABPM from baseline	AZL 80 mg (–14.6) significantly improved mean SBP vs OLM (–12.6) ($p = 0.038$); 40 mg (–13.5) were noninferior
White (2011)[19]	R, DB, PC, parallel	1291	Clinic SBP 150-180 mm Hg and 24-hour mean SBP 130-170 mm Hg	AZL 40, 80 mg once daily vs OLM 40 mg once daily vs VAL 320 mg once daily vs Placebo	6 weeks	Change in 24-hour mean SBP by ABPM from baseline	AZL 80 mg (–14.5 ± 0.7) significantly improved mean SBP more than OLM (–11.7 ± 0.7) and VAL (–10.2 ± 0.7) ($p = 0.009$ for both); AZL 40 mg (–13.4 ± 0.7) noninferior to OLM
Sica (2011)[20]	R, DB, PC, parallel	984	Clinic SBP 150-180 mm Hg and 24-hour mean SBP 130-170 mm Hg	AZL 40, 80 mg once daily vs VAL 320 mg once daily	24 weeks	Change in 24-hour mean SBP by ABPM from baseline	AZL 40 mg (–14.9) and 80 mg (–15.3) significantly improved 24-hour mean SBP more than VAL (–11.3; $p < 0.0001$ for both)

ABPM = ambulatory blood pressure monitoring; AZL = azilsartan medoxomil; DB = double-blind; OLM = olmesartan; PC = placebo-controlled; R = randomized; SBP = systolic blood pressure; VAL = valsartan.

20-mg or 80-mg groups were not available. These results suggest that azilsartan medoxomil 80 mg is superior to olmesartan at reducing both SBP and DBP using either ambulatory BP monitoring (ABPM) or clinic readings, with similar tolerability.

White and colleagues evaluated azilsartan medoxomil versus olmesartan and valsartan in 1291 patients with stage 1 and 2 hypertension.[19] Therapy was initiated with half doses and titrated up to the target dose after 2 weeks. Mean baseline clinic BPs were 156-158/92-93 mm Hg, and baseline 24-hour mean BPs were 144-146/88-90 mm Hg. Significantly greater reductions in mean 24-hour SBP were seen with azilsartan medoxomil 80 mg versus both olmesartan ($p = 0.009$) and valsartan ($p < 0.001$), whereas the azilsartan medoxomil 40-mg dose was noninferior to olmesartan (Figure 2). Similar findings were seen in changes from baseline in clinic SBP, 24-hour mean DBP, and clinic DBP. When evaluating the ABPM findings, azilsartan medoxomil 80 mg had lower SBP readings at most time points than either valsartan or olmesartan, suggesting its potential to provide greater 24-hour BP control. In contrast to the results of Bakris and colleagues,[18] a significantly greater proportion of patients in the azilsartan medoxomil 80-mg group were considered responders (58%) (defined as either reaching a clinic SBP target of <140 mm Hg and/or a >20 mm Hg reduction in SBP from baseline) than placebo (22%), valsartan (49%), and olmesartan (49%) ($p < 0.05$ for all).[19]

The most recently published study[20] extended the study duration to 24 weeks as opposed to the 2 previously discussed 6-week trials.[18,19] Sica and colleagues randomized 984 patients to receive azilsartan medoxomil or maximum-dose valsartan.[20] Baseline clinic SBP ranged from 157.0 ± 14.0 mm Hg with valsartan to 158.1 ± 14.4 mm Hg and 156.3 ± 12.5 mm Hg with azilsartan medoxomil 40 mg and 80 mg, respectively. Changes from baseline in 24-hour mean SBP were significantly greater for both the azilsartan medoxomil 40-mg (–14.9) and 80-mg (–15.3) groups versus valsartan (–11.3; $p < 0.001$ for both). Similar patterns of response were seen in clinic SBP, as well as 24-hour mean DBP and clinic DBP. The proportion of patients considered responders was significantly lower with valsartan 320 mg (47%) compared with azilsartan medoxomil 40 mg (56%; $p = 0.016$) or 80 mg (59%; $p = 0.002$).

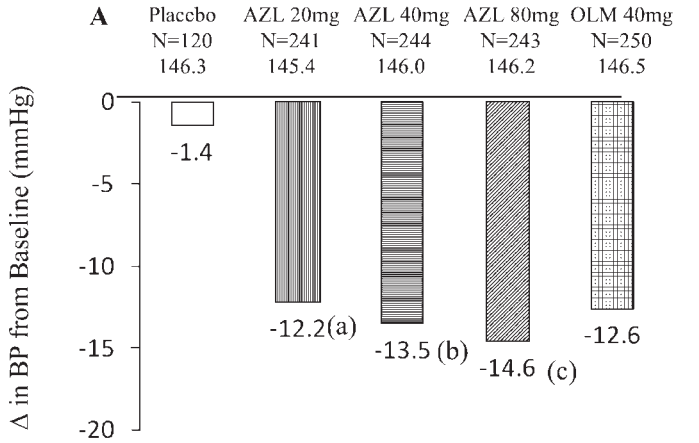
Table 3. Azilsartan Clinical Trials Available in Abstract Only

Reference	Design	Pts. (N)	Inclusion Criteria	Dosage	Duration	Primary Outcome	Results
Bonner[21] (2010)	R, DB, parallel	884	Clinic SBP 150-180 mm Hg	AZL 40, 80 mg once daily vs RAM 10 mg once daily	24 weeks	Change in trough sitting clinic SBP from baseline	AZL 40 mg (–20.6 ± 0.9) and 80 mg (–21.2 ± 0.9) significantly improved clinic SBP more than RAM (–12.2 ± 0.9) ($p < 0.001$ for both)
Weber[22] (2010)	R, DB, PC, parallel	562	Stage 2 hypertension	AZL 40, 80 mg once daily + AML 5 mg once daily vs AML 5 mg once daily + placebo	6 weeks	Change in 24-hour mean SBP by ABPM from baseline	AZL 40 mg and 80 mg + AML 5 mg significantly reduced 24-hour mean SBP vs AML + placebo ($p < 0.001$ for both)
Sica[23] (2010)	R, DB, PC, parallel	448	Stage 2 hypertension	AZL 40, 80 mg once daily + CLD 25 mg once daily vs Placebo + CLD 25 mg once daily	6 weeks	Change in 24-hour mean SBP by ABPM from baseline	AZL 40 mg + CLD (–31.7) and 80 mg + CLD (–31.3) significantly improved mean SBP more than placebo + CLD (–15.9) ($p < 0.001$ for both)
Sica[24] (2011)	R, DB, parallel	1714	Clinic SBP 160-190 mm Hg	AZL 0, 20, 40, 80 mg once daily + CLD 0, 12.5, 25 mg once daily vs AZL 20, 40, 80 mg CLD 0, 12.5, 25 mg once daily	8 weeks	Change in trough SBP by 24-hour ABPM from baseline	Each AZL/CLD FDC reduced trough SBP significantly more than CLD or AZL alone ($p < 0.001$ for all)
Cushman[25] (2011)	R, DB, parallel	1085	Clinic SBP 160-190 mm Hg + DBP ≤119 mm Hg	AZL 20, 40 mg once daily + CLD 12.5, 25 mg once daily vs OLM 20, 40 mg once daily + HCTZ 12.5, 25 mg once daily	8 weeks	Change in clinic seated trough SBP from baseline	AZL/CLD FCDs reduced clinic SBP significantly more than OLM/HCTZ FDCs ($p < 0.001$ for each)

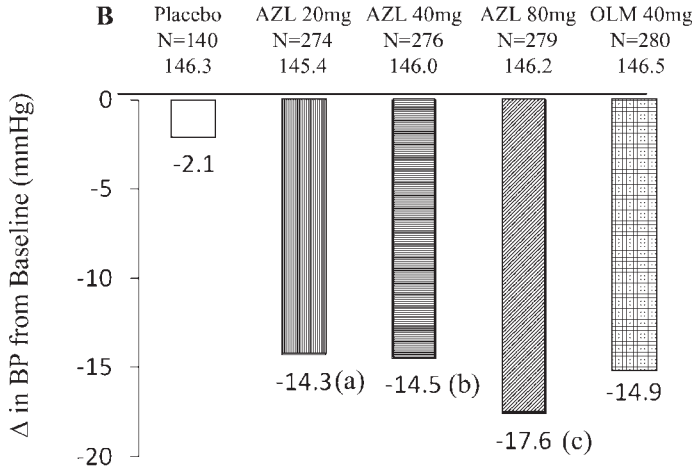
ABPM = ambulatory blood pressure monitoring; AML = amlodipine; AZL = azilsartan; CLD = chlorthalidone; DB = double-blind; DBP = diastolic blood pressure; FDC = fixed-dose combinations; HCTZ = hydrochlorothiazide; OLM = olmesartan; PC = placebo-controlled; R = randomized; RAM = ramipril; SBP = systolic blood pressure.

These 3 pivotal clinical trials demonstrated the ability of azilsartan medoxomil across the dose range of 40-80 mg daily to lower both 24-hour SBP as measured by ABPM and trough sitting clinic SBP versus both olmesartan and valsartan, each given at their respective maximal doses over a 6- to 24-week period.[18-20] The comparisons made in these studies are clinically relevant, as olmesartan had been shown to reduce BP significantly more than older ARBs, including losartan and irbesartan.[26]

A unique feature of the azilsartan medoxomil clinical studies is the use of 24-hour SBP as the primary efficacy measurement to evaluate the comparative effects of azilsartan medoxomil with other antihypertensives. There are theoretical advantages to using ABPM to assess a new antihypertensive drug. First, ABPM is superior in assessing the trough-to-peak ratio of antihypertensive medications compared to the clinic BP[27] and has been shown to be a more reliable predictor of cardiovascular outcomes compared with traditional clinic or office BP readings.[28,29] Second, using ABP-derived values both as inclusion criteria as well as endpoint evaluation avoids inclusion of patients with proposed white-coat hypertension, which can skew clinic BP readings in clinical trials.[30] Moreover, ABPM produces lower variance with repeated studies compared with clinic BP measures and, from a clinical trials standpoint, allows for lower numbers of patients to be required to show the desired effect size of the drug under study.[31,32] Notable exclusion criteria from each of the azilsartan medoxomil trials included patients with a history of major cardiovascular events or significant cardiac conduction abnormalities, severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2), or type 1 or poorly controlled type 2 diabetes. Thus, the trial results cannot be applied directly to these populations. This is particularly important since many patients with hypertension requiring large reductions in SBP to achieve their desired goal have cardiovascular disease and there is a lack of efficacy or safety data for azilsartan medoxomil in these populations. Given the known clinical profiles of other ARBs in major outcome trials, alternative choices in patients with either cardiovascular disease or diabetic renal disease may be appropriate.[4,5]



(a) p<0.001 vs. placebo; p=0.687 vs. OLM
(b) p<0.001 vs. placebo; p=0.352 vs. OLM
(c) p<0.001 vs. placebo; p=0.038 vs. OLM



(a) p<0.001 vs. placebo; p=0.662 vs. OLM
(b) p<0.001 vs. placebo; p=0.768 vs. OLM
(c) p<0.001 vs. placebo; p=0.043 vs. OLM

Figure 1. Comparison of azilsartan versus olmesartan on 24-hour mean (A) and sitting trough clinic (B) systolic BP. AZL = azilsartan; BP = blood pressure; OLM = olmesartan. Modified with permission.[18]

ABSTRACT-ONLY STUDIES

Several clinical studies with azilsartan medoxomil have been published only in abstract form (Table 3). These studies include comparisons of azilsartan medoxomil with ACE inhibitors,[21] combinations with calcium channel blockers[22] and diuretics[23-25] and its use in different populations, such as African Americans.[33] A study of 884 patients showed significant reductions in trough sitting clinic SBP from baseline (range 160.9-161.5 mm Hg) with both azilsartan medoxomil 40 mg (–20.6 ± 0.9 mm Hg) and 80 mg (–21.2 ± 0.9 mm Hg) versus ramipril (–12.2 ± 0.9 mm Hg) ($p < 0.001$ for both azilsartan doses).[21] Response rates for both SBP and DBP were also significantly

higher with azilsartan medoxomil 40 and 80 mg (54.0% and 53.6%, respectively) versus ramipril (33.8%, $p < 0.001$ for both).

Azilsartan medoxomil has also been evaluated in combination with other antihypertensive agents. A study of 562 patients showed that amlodipine plus azilsartan medoxomil 40 mg (–24.8/–15.3 mm Hg) and 80 mg (–24.5/–15.4 mm Hg) reduced 24-hour SBP/DBP, measured by ABPM, to a greater extent than amlodipine alone (–13.6/–7.8 mm Hg) ($p < 0.001$ for both).[22] Moreover, response rates for both SBP and DBP for the combination (66% and 69%, respectively) were higher than those with the single agent (43%). This investigation is of particular clinical relevance given the recent data showing outcome benefits when combining blockers of the renin-angiotensin-aldosterone system with a calcium channel blocker as opposed to with a thiazide diuretic (hydrochlorothiazide).[34]

Three other studies published in abstract form compared the combination of azilsartan medoxomil plus the thiazide-like diuretic chlorthalidone as a fixed-dose combination versus either monotherapy[23,24] or the combination of olmesartan plus hydrochlorothiazide.[25] The choice of chlorthalidone as the diuretic for these investigations is notable, given the recently published data suggesting improved BP control (on a milligram-to-milligram basis) and improved outcomes as compared with hydrochlorothiazide.[35,36] These studies show that combining azilsartan medoxomil with chlorthalidone produces significant reductions in 24-hour mean SBP across a number of dosing combinations (Table 3) compared with chlorthalidone alone.[23,24] Furthermore, this combination significantly reduced clinic SBP to a greater degree than the combination of olmesartan plus hydrochlorothiazide (Figure 3).

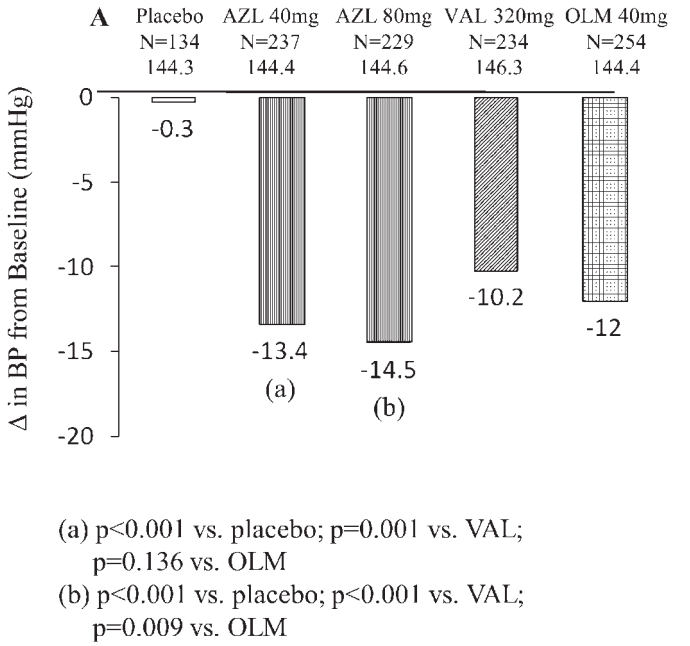


Figure 2. Comparison of azilsartan versus olmesartan or valsartan on 24-hour mean (A) and sitting trough clinic (B) systolic BP in stage I and II hypertension.[19] AZL = azilsartan; BP = blood pressure; OLM = olmesartan; VAL = valsartan.

Adverse Events

ARBs have been shown to have tolerability similar to that of placebo and other antihypertensive drug classes.[37,38] This favorable adverse event profile likely explains the greater adherence rates over years of use compared with other agents.[39] Data from the 3 published clinical trials show similar tolerability of azilsartan medoxomil to placebo[18,20] and other ARBs.[18-20] The most commonly reported adverse events with azilsartan medoxomil included headache, dizziness, urinary tract infections, and fatigue, all occurring in less than 10% of patients and at rates similar to those with placebo. The rate of adverse events leading to study medication discontinuation with azilsartan medoxomil 40 mg and 80 mg ranged from 1.1-7.0% and 2.1-8.2% versus 1.9-4.2% with placebo to 1.4-2.1% with olmesartan 40 mg and 1.1-6.1% with valsartan 320 mg. Statistical comparisons between these groups are not available. Hyperkalemia, defined as a serum potassium level

higher than 6.0 mEq/L, did not occur in any patients in the study by White and colleagues[19] and was reported in 1.8% and 0.3% of patients in the azilsartan medoxomil 40-mg and 80-mg arms, respectively, by Sica and colleagues[20] versus 0.6% in the valsartan 320-mg arm. Other laboratory findings, such as increases in serum creatinine or liver enzyme levels, occurred infrequently and at similar rates between all groups compared across studies. Of the 3550 patients included in the 3 published studies, 2 deaths occurred in the azilsartan medoxomil group[18,20] and 1 occurred in the valsartan 320-mg group.[20] Whether these deaths could be attributed to the study drug was not made clear.

The safety and tolerability data for azilsartan medoxomil combined with other antihypertensive agents are available only in the studies published in abstract form, thus providing relatively little information. The incidences of hypotension and elevations in serum creatinine from baseline were higher with azilsartan medoxomil plus chlorthalidone versus chlorthalidone alone, while hypokalemia occurred less frequently with combination use.[20] The rate of peripheral edema was lower when azilsartan medoxomil was combined with amlodipine (2.1%) versus amlodipine alone (4.9%).[22] A more detailed review of the safety and tolerability of combination therapies with azilsartan medoxomil will have to wait until the full publications of these studies are made available.

Dosage Considerations

Azilsartan medoxomil is supplied as a white, unscored tablet for oral use with recommendations to retain the medication in its original manufacturer's container and protect it from light and moisture.[11] It has been approved by the FDA to lower blood pressure in patients with hypertension and should be given as 80 mg orally once daily, without regard to food, with the lower dose (40 mg once daily) given to patients treated with high-dose diuretics. No dosage adjustments are recommended for special populations, including elderly patients, those with renal impairment (mild-to-moderate and end-stage), and mild-to-moderate hepatic impairment.[11] Data from studies available only in abstract form suggest that azilsartan medoxomil can be combined with either the calcium channel blockers (eg, amlodipine) or thiazide diuretics (eg, chlorthalidone) in patients who require additional BP lowering to achieve their goal.[22-25] The manufacturer is also anticipated to market a fixed-dose combination of azilsartan-chlorthalidone because of its large BP-lowering effects, potentially obviating the need for other agents. This could pose both BP benefit and an adherence benefit for patients with stage 2 hypertension. Information from the manufacturer (Takeda Pharmaceuticals, Inc.) on the cost of azilsartan medoxomil suggests that the average wholesale price of the 40-mg and 80-mg dosage forms will be $2.94 per tablet.[40] As a comparison, valsartan 320 mg is $4.40 per dose and olmesartan 40 mg is $4.40 per dose. Thus, the daily cost of azilsartan medoxomil may be less than that of the ARBs used in available head-to-head clinical trials. There are drugs in this class that are generically available (losartan potassium, 100 mg costs $3.08 per dose) and others that are anticipated to become available in the next year (valsartan).[40] Data evaluating the cost-effectiveness of azilsartan medoxomil versus other ARBs is lacking and would be of high interest to third-party payers and those involved with formulary decision-making.

Similar to other ARBs, azilsartan medoxomil use should be avoided in women who become pregnant.[41] It should

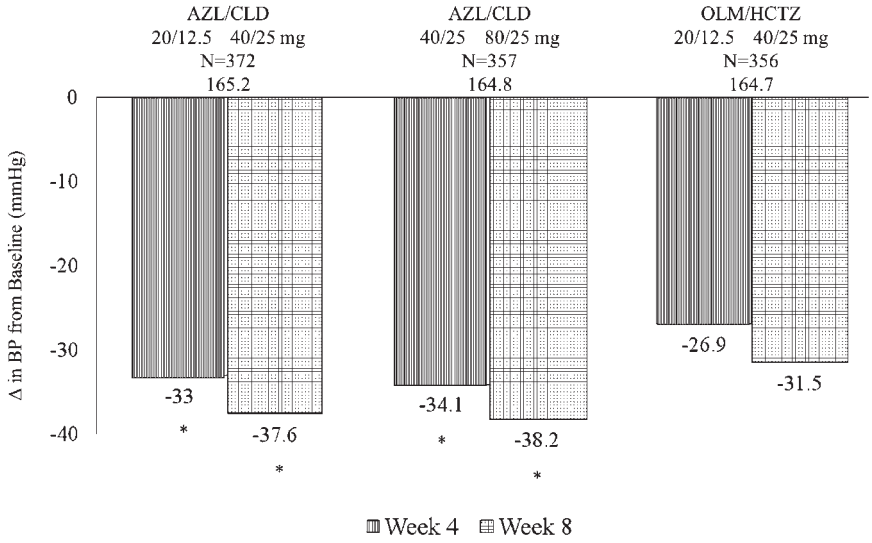


Figure 3. Combination of azilsartan/chlorthalidone versus olmesartan/hydrochlorothiazide on systolic BP in stage I and II hypertension.[25] AZL = azilsartan; BP = blood pressure; CLD = chlorthalidone; HCTZ = hydrochlorothiazide; OLM = olmesartan. *p < 0.001 vs OLM/HCTZ.

also be used with caution, and withheld or dose-reduced, in patients experiencing symptomatic hypotension in the presence of appreciable volume or salt depletion. Similar precautions are given in the manufacturer's prescribing information related to patients with impaired renal function and heart failure, renal artery stenosis, or volume depletion because of a risk of acute worsening when azilsartan medoxomil is initiated.[11]

The exact role that azilsartan medoxomil will have in clinical practice is unclear. Although clinical studies have shown that 80 mg (recommended starting dose) will lower BP to a greater extent than other available ARBs, information demonstrating reduction of clinical outcomes with azilsartan medoxomil is lacking, and that is unlikely to change in the near future. Alternatively, a number of other ARBs have robust clinical data showing outcome reduction. As an example, the CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) studies demonstrated significant reductions in cardiovascular deaths ($p = 0.012$) and heart failure hospitalizations ($p < 0.0001$) with candesartan versus placebo in patients receiving concomitant diuretic and β-blocker therapy.[42] Two large clinical trials have shown beneficial effects of telmisartan on major outcomes compared with placebo[43] and similar effects to the ACE inhibitor ramipril.[44] The FDA recently added wording to the package inserts of some ARBs, including azilsartan medoxomil, discussing reductions in major outcomes, such as fatal and nonfatal myocardial infarction and stroke. Given this labeling change and the well-recognized effects of BP lowering in certain disease states, it is unclear whether large outcome-based trials of azilsartan medoxomil will be conducted or required.

A review of www.clinicaltrials.gov was conducted to identify pertinent ongoing clinical trials with azilsartan medoxomil involving patients in the US. One trial (NCT01309828), scheduled to be completed in early 2013, is evaluating the safety and tolerability of combination azilsartan medoxomil plus chlorthalidone versus olmesartan plus hydrochlorothiazide in patients with hypertension and concomitant kidney disease. This is a BP lowering and general safety study and is not evaluating renal outcomes such as time to dialysis or development of end-stage renal failure. A second trial (NCT01078376) is evaluating the use of azilsartan medoxomil in pediatric populations with hypertension and is scheduled to be completed in mid-2012. No other studies evaluating the impact of azilsartan medoxomil on cardiovascular outcomes were identified.

Formulary Recommendation

Based on the currently available evidence, it seems prudent to add azilsartan medoxomil to relevant formularies for the treatment of patients with hypertension. Given the efficacy and safety data compared with other currently available ARBs in addition to the anticipated approval of a combination product with chlorthalidone, this agent offers clinical practitioners a potent antihypertensive option that can aid in getting their patients to goal.

Summary

Azilsartan medoxomil is a highly specific, potent ARB that is FDA-approved to lower blood pressure in patients with hypertension. Its pharmacologic profile suggests that it may offer advantages over other currently available ARBs. Direct comparative studies have demonstrated the ability of azilsartan medoxomil to reduce BP to a greater extent than other available ARBs, including valsartan and olmesartan. However, not all studies enrolled patients with a history of major cardiovascular disease, significant renal disease, or diabetes mellitus. The observed benefits on either 24-hour mean SBP or sitting trough clinic SBP with azilsartan medoxomil versus other ARBs may be related to its pharmacologic profile, including slowed AT_1-receptor dissociation rates and improved receptor specificity. Data detailing whether these properties lead to reductions in clinical outcomes are not available. The drug is available as a 40-mg and 80-mg tablet and can be given once daily without regard to meals. The FDA recommends 80 mg as the initial dose of azilsartan medoxomil, with 40 mg being reserved for patients on high-dose diuretics. The lack of clinically significant drug interactions is an added benefit to its use. The continued study of azilsartan medoxomil in different patient populations (eg, diabetes mellitus, chronic kidney disease) could aid in further identifying where it fits in contemporary medical management.

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Conflict of interest: Dr. White's Division has received research funding from Takeda Global Research and Development, the manufacturer of azilsartan medoxomil, between 2007 and 2009. Dr. White is a paid safety consultant to Takeda for chairing the adjudication committee of the febuxostat cardiovascular outcomes study and chairs the Steering Committee for the EXAMINE trial, an evaluation of the cardiovascular safety of alogliptin.

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Azilsartan Medoxomilo: Un Antagonista de los Receptores de Angiotensina II Nuevo para el Tratamiento de Hipertensión

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Ann Pharmacother 2011;45:1506-15.

EXTRACTO

OBJETIVO: Evaluar la eficacia, seguridad y el papel clínico de azilsartan medoxomilo, un bloqueador de los receptores de angiotensina II (ARB) el cual recientemente obtuvo aprobación por la Administración de Drogas y Alimentos para bajar la presión sanguínea (BP) en pacientes con hipertensión.

FUENTES DE INFORMACIÓN: Se realizó una revisión sistémica de la literatura a lo largo del mes de agosto 2011 utilizando el sistema MEDLINE, Web de la Ciencia, y los *Resúmenes Farmacéuticos Internacionales* utilizando las palabras claves y títulos médicos relacionados a azilsartan, azilsartan medoxomilo, TAK-491, TAK-536 y Edarbi. Los resúmenes presentados en los pasados 2 años en reunión anual de varias sociedades médicas fueron revisados, en adición a una búsqueda en clinicaltrials.gov.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODOS DE EXTRACCIÓN DE INFORMACIÓN: Citaciones elegibles para inclusión fueron evaluaciones de azilsartan medoxomilo en-vitro o en-vivo sin restricción alguna en la población de pacientes o indicación utilizada. Los datos relacionados a las poblaciones de pacientes y resultados de interés fueros extraídos de cada citación.

SÍNTESIS: Tres estudios están disponibles en la forma de publicación completa, con otros disponibles sólo como resúmenes. Azilsartan medoxomilo 40 mg y 80 mg diarios mejoró significativamente ambas presiones sanguíneas de base, sistólica y diastólica, comparado con placebo y la dosis de 80 mg tiene mayor eficacia que otros ARBs incluyendo olmesartan 40 mg diarios y valsartan 320 mg diarios. Mejoría tanto en la BP en 24 horas, utilizando monitoreo ambulatorio y BPs obtenidas en la clínica, se ha observado con azilsartan medoxomilo así como una proporción más alta de pacientes que alcanzan la meta. Información adicional muestra que cuando azilsartan medoxomilo se combina con clortalidona hay una baja aditiva en BP. Los eventos adversos son similares con azilsartan medoxomilo comparado con otros ARBs, e incluyen dolor de cabeza, mareos, infecciones del tracto urinario y fatiga.

CONCLUSIONES: Azilsartan medoxomilo es un ARB seguro y efectivo con un perfil farmacocinético único comparado con otros agentes, incluyendo velocidades de disociación del receptor AT1 bajas y especificidad mejorada del receptor. Estudios han demostrado que 80 mg de azilsartan medoxomilo diarios reduce la BP en mayor medida que valsartan y olmesartan con una seguridad y tolerabilidad similar.

Traducido por Jennifer Guzmán

Le Medoxomil d'Azilsartan: un Nouvel Antagoniste des Récepteurs de l'Angiotensine II Pour le Traitement de l'Hypertension

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Ann Pharmacother 2011;45:1506-15.

RÉSUMÉ

OBJECTIF: Évaluer l'efficacité, l'innocuité et le rôle du medoxomil d'azilsartan, un nouveau bloqueur des récepteurs de l'angiotensine II (BRA) récemment approuvé par la FDA des États-Unis d'Amérique pour réduire la tension artérielle (TA) chez les patients hypertendus.

PROVENANCE DES DONNÉES: Une revue systématique de la littérature médicale publiée en date d'août 2011 a été effectuée via MEDLINE, Web of Science, et *International Pharmaceutique Résumé* en utilisant les termes azilsartan, azilsartan medoxomil, TAK-491, TAK-536, et Edarbi. Les résumés de communications présentées au cours des 2 dernières années dans le cadre de réunions annuelles de plusieurs sociétés savantes ont été revus, de même que le site clinicaltrials.gov.

SÉLECTION DES DONNÉES: Les études portant sur l'évaluation du medoxomil d'azilsartan, que ce soit in-vitro ou in-vivo, ont toutes été retenues peu importe la population ou l'indication étudiée. Les données relatives à la population de patients et les résultats pertinents ont été extraits de chaque publication retenue.

RÉSUMÉ: Trois études étaient disponibles sous forme de publication complète, toutes les autres n'étaient disponibles que sous forme de résumé. Le medoxomil d'azilsartan en dose journalière de 40 mg à 80 mg améliore significativement la tension systolique et diastolique par rapport à un placebo. Une dose de 80 mg par jour s'est avérée plus efficace pour contrôler la TA que 40 mg d'olmesartan ou 320 mg de valsartan. Ces améliorations portaient autant sur la TA mesurée en clinique que sur celle mesurée en monitorage ambulatoire de 24 heures ou encore sur la proportion de patients atteignant un niveau cible. L'effet est augmenté par l'addition de chlorthalidone. Les effets indésirables du medoxomil d'azilsartan medoxomil sont similaires à ceux des autres BRA, soit les maux de tête, les étourdissements, les infections du tractus urinaire, et la fatigue.

CONCLUSIONS: Le medoxomil d'azilsartan est un BRA sûr et efficace pour le contrôle de la TA chez les patients hypertendus. Son profil pharmacologique unique, en particulier une vitesse de dissociation lente des récepteurs AT1 et une meilleure spécificité aux récepteurs, suggère qu'il pourrait offrir certains avantages par rapport autres BRA présentement disponibles. Les études ont démontrés une efficacité supérieure aux autres BRA tels que le valsartan et l'olmesartan et un profil d'innocuité similaire. Des études liant ces avantages aux résultats thérapeutiques tels que les complications cardio-vasculaires et la mortalité manquent encore.

Traduit par Suzanne Laplante