EXPERT OPINION

Pharmacokinetic evaluation and clinical utility of azilsartan medoxomil for the treatment of hypertension

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Introduction: Azilsartan medoxomil is a newly approved angiotensin-receptor blocker for the management of hypertension. It is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and highly selective angiotensin-receptor blocker with estimated bioavailability of ~ 60%. This new agent induces a potent and long-lasting antihypertensive effect. The effective therapeutic antihypertensive dosages of azilsartan medoxomil in humans vary from 40 to 80 mg/day.

Areas covered: The authors review the results of clinical trials published in journals indexed in Medline, Scopus and Google Scholar. Primarily the authors discuss articles that analyze the safety and efficacy of azilsartan in lowering blood pressure.

Expert opinion: Clinical trials have demonstrated that azilsartan is superior to other angiotensin-receptor blockers in lowering blood pressure. However, the clinical blood pressure trials of azilsartan published to date have been mainly conducted in patients without serious comorbidities and it is not clear if azilsartan has advantages over other angiotensin-receptor blockers in the treatment of these types of hypertensive patients. In addition, it remains to be determined whether the specific pharmacologic and pharmacokinetic characteristics of azilsartan will have a clinically significant impact on long-term cardiovascular outcomes.

Keywords: azilsartan medoxomil, blood pressure, efficacy, hypertension, safety, treatment

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1. Introduction

Increased activity of the renin–angiotensin–aldosterone system (RAAS) plays a major role in the development and progression of hypertension and related cardiovascular (CV) complications [1-4].

Angiotensin II is the major effector hormone of the RAAS and exhibits a key role in the regulation of blood pressure (BP), fluid-electrolyte balance and pathophysiology of hypertension.

The numerous effects of angiotensin II, including vasoconstriction, cellular proliferation, cardiomyocyte hypertrophy, vascular smooth muscle migration and proliferation, inflammation and platelet aggregation, are dominantly mediated primarily through the activation of the angiotensin type 1 (AT_1) receptor subtype [1-6].

Therefore, an angiotensin II receptor blocker (ARB) that blocks AT_1 receptors is a logical therapeutic strategy in the management of hypertension and CV complications.

Until recently, there were seven ARBs available on the market. All are approved for the treatment of hypertension and some are also indicated for the management of congestive heart failure, hypertensive target organ damages and diabetic nephropathy (**Table 1**).

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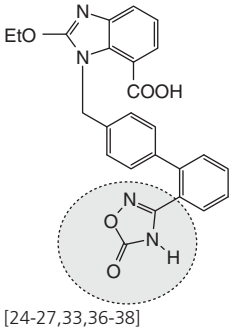
Box 1. Drug summary.

Drug name (generic)	Azilsartan medoxomil
Phase (for indication under discussion)	Launched
Indication (specific to discussion)	Hypertension
Pharmacology description/mechanism of action	Antagonist of angiotensin II type 1 receptors
Route of administration	for once daily orally administration
Chemical structure	
Pivotal trial(s)	[24-27,33,36-38]

The chemical structure of azilsartan is identical to the structure of candesartan except that azilsartan has a 5-oxo-1,2,4-oxadiazole ring (grey area) in place of the tetrazole ring found in candesartan

Azilsartan medoxomil (**Box 1**) [7] is the eighth ARB that recently gained approval from the US Food and Drug Administration for lowering the BP in patients with hypertension.

We evaluated the pharmacokinetic properties of azilsartan and we critically reviewed the results of clinical studies investigating the safety and efficacy of this agent in reducing BP.

Relevant data were identified from journals indexed in Medline, Scopus and Google Scholar using search the terms 'Azilsartan, TAK-491, TAK-536, angiotensin receptor blockers, pharmacology, pharmacokinetics, pharmacodynamics, hypertension, blood pressure and safety'. We also performed hand-searching of conference proceedings, pharmaceutical industry files and personal communication from experts in the field, to identify any other relevant study.

No language restriction was applied, to avoid discriminating papers not written in the English language.

2. Pharmacodynamic and pharmacokinetics

Azilsartan medoxomil (TAK-491) is chemically described as (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylatemonopotassium salt. Its empirical formula is $C_{30}H_{23}KN_4O_8$.

Azilsartan medoxomil is the prodrug of the active moiety, azilsartan (TAK-536), a potent and selective antagonist of AT_1 receptors [8,9].

After oral administration, azilsartan medoxomil is rapidly converted to azilsartan by ester hydrolysis in the gut and/or during the process of absorption. Azilsartan medoxomil is mostly absorbed from the jejunum, duodenum and ileum and is poorly absorbed from the stomach and colon [8,10].

Azilsartan achieves its peak plasma concentration 1.5 to 3 h following oral administration, with bioavailability (~ 58%) unaffected by coadministration with food [11,12].

Azilsartan demonstrates a half-life of ~ 11 h and achieves a steady-state concentration 5 days following consecutive oral administration. The volume of distribution of azilsartan is ~ 30 L in healthy subjects and it is almost completely (99%) bound to plasma proteins. Distribution of azilsartan in red blood cells is 2% and is concentration independent (0.3 – 30 µg/mL).

Notably, Azilsartan has high affinity for AT_1 receptors and is > 10,000-fold more selective for AT_1 receptors compared with angiotensin II type 2 (AT_2) receptors *in vitro* (**Table 1**) [11-13].

Azilsartan is mainly metabolized in the liver via cytochrome P450 2C9 (CYP2C9) to its inactive metabolite, M-II (formed by *O*-dealkylation). Azilsartan is also metabolized to a smaller extent by CYP2B6 and CYP2C8 to another inactive metabolite, M-I (formed by decarboxylation).

Azilsartan is primarily excreted in the urine as inactive metabolites. The renal clearance of azilsartan is 2.3 mL/min [12,14].

Animal studies recording 14C-radiolabeled orally administered azilsartan recovered ~ 97% of the administered dose within 14 days. Specifically, 55% was traced to fecal excretion, and urine accounted for 42%, of which 15% was excreted as azilsartan [12,14].

No studies regarding the pharmacokinetics of azilsartan are currently available. However, the data reporting a dose proportionality following single- and multiple-dosing of azilsartan in the dose range of 20 – 320 mg has been made available by the manufacturer [14]. According to single- and multiple-dose studies, pharmacokinetic properties of azilsartan is modestly affected by age, sex, race, renal impairment and low or hepatic impairment. Accordingly, no dosage adjustment of azilsartan is suggested on the basis of a patient's age, gender, race, or degree of renal/hepatic impairment [14].

As other ARBs, the prescribing information for azilsartan includes a boxed warning to discontinue use when a patient becomes pregnant, due to the risk of fetal injury and death.

3. Comparison with other ARBs

Numerous comparative clinical trials have recently suggested differences in BP control among different ARBs [15]. These drugs share a common mechanism of action-antagonism of angiotensin II AT_1 receptors; in particular, ARBs possess common structural features that are required for effective antagonism of the AT_1 receptor.

However, their receptor-binding kinetics differs resulting in differential pharmacological potency and efficacy.

ARBs are generally classified as surmountable or insurmountable antagonists on the basis of functional data, such

Table 1. Main characteristics of the eight ARBs available on the market.

Chemical name	Half-life (h)	Receptor selectivity (AT_1/AT_2)	Pressor inhibition at 24 h	Indication
Azilsartan	11	> 10,000-fold	40 mg: 60%	Hypertension
Candesartan	9	> 10,000-fold	8 mg: 50%	Hypertension, heart failure
Eprosartan	20	1,000-fold	350 mg: 30%	Hypertension
Irbesartan	11-15	> 8,500-fold	150 mg: 40% 300 mg: 60%	Hypertension, diabetic nephropathy
Olmesartan	13	> 12,500-fold	20 mg: 61% 40 mg:: 74%	Hypertension
Losartan	2	1,000-fold	100 mg: 25 – 40%	Hypertension, diabetic nephropathy
Valsartan	6	20,000-fold	80 mg: 30%	Hypertension, heart failure, myocardial infarction
Telmisartan	24	> 3,000-fold	80 mg: 40%	Hypertension

as angiotensin II-mediated contractions in isolated vascular tissues [16].

Candesartan has a higher affinity for the AT_1 receptor than all the other ARB. In addition, candesartan and irbesartan block the AT_1 receptor with insurmountable antagonism, whereas losartan, valsartan and eprosartan are competitive antagonists.

The insurmountable inhibition by some ARBs might be due to slow dissociations from AT_1 receptors and has been proposed to contribute to the long-lasting clinical actions [17]. Indeed, results of comparative clinical trials suggest that insurmountable ARBs, such as candesartan cilexetil and olmesartan medoxomil, may be more effective than the surmountable antagonist losartan or the partially insurmountable antagonists valsartan and irbesartan in reducing the BP of patients with mild-to-moderate hypertension [18-21].

Azilsartan [22] is structurally similar to candesartan except that it bears a 5-oxo-1,2,4-oxadiazolemoiety in place of the tetrazole ring. Azilsartan has a carboxyl group at the 7-position of the benzimidazole ring, which is the group that is believed to have a role in producing the insurmountable receptor antagonistic activity of candesartan [23]. This insurmountable binding of azilsartan to the AT_1 receptor may contribute to its potent and long-lasting antihypertensive activity.

In this context, Ojima *et al.* [13] recently investigated the angiotensin II antagonistic properties of azilsartan in binding studies and in a cell-based assay using human AT_1 receptors and in contraction studies using rabbit aortic strips. In both binding studies and the cell-based assay, they evaluated the dissociation of azilsartan and other ARBs (olmesartan, telmisartan, valsartan and irbesartan) from AT_1 receptors after the removal of the compounds by washout.

They demonstrated that azilsartan is a selective and insurmountable AT_1 receptor antagonist with a high affinity to AT_1 receptors. It remained substantially bound to the receptors after washout of the compound compared with other ARBs. Furthermore, the inhibitory effects of azilsartan on vasoconstriction induced by angiotensin II persisted even after washout, whereas those of other ARBs were markedly attenuated.

4. BP lowering effect

Several comparative studies have assessed the efficacy of azilsartan in the treatment of hypertension.

Four studies [24-27] comparing the efficacy of azilsartan with other ARBs have been published in the literature to date (**Figure 1**). These multicenter studies recruited patients with primary hypertension and used ambulatory BP measurements [28-32]. Overall, azilsartan medoxomil at a dose of 80 mg/day showed superior efficacy to the top approved doses for hypertension of olmesartan, valsartan and candesartan [24-27].

A 24-week, randomized, double-blind study was also conducted to compare the antihypertensive efficacy and safety of azilsartan medoxomil with that of ramipril [33]. The comparison of aliskiren with ramipril is of particular interest. It has been argued that ramipril is an appropriate benchmark to test the potential clinical benefits of new antihypertensive drugs. The antihypertensive efficacy of ramipril has been confirmed in large-scale non-comparative studies conducted in general practice as well as in more rigorously controlled clinical trials [34]. In addition, in the Heart Outcomes Prevention Evaluation (HOPE) trial [35], ramipril significantly reduced CV morbidity and mortality in patients at high risk for CV events.

Patients included in this study were randomly assigned to receive daily doses of azilsartan medoxomil 20 and 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. The primary efficacy endpoint was the change in clinic and ambulatory systolic BP from baseline. Secondary endpoints included response rates (i.e., clinic systolic and diastolic BP below 140/90 mmHg and/or a reduction of 20/10 mmHg or more from baseline) and safety parameters [33].

Azilsartan medoxomil 40 and 80 mg reduced both clinic and mean 24-h systolic BP significantly more than did ramipril 10 mg (-20.6 ± 0.9, -21.2 ± 0.9 and -12.2 ± 0.9, respectively). Response rates were also significantly greater with azilsartan

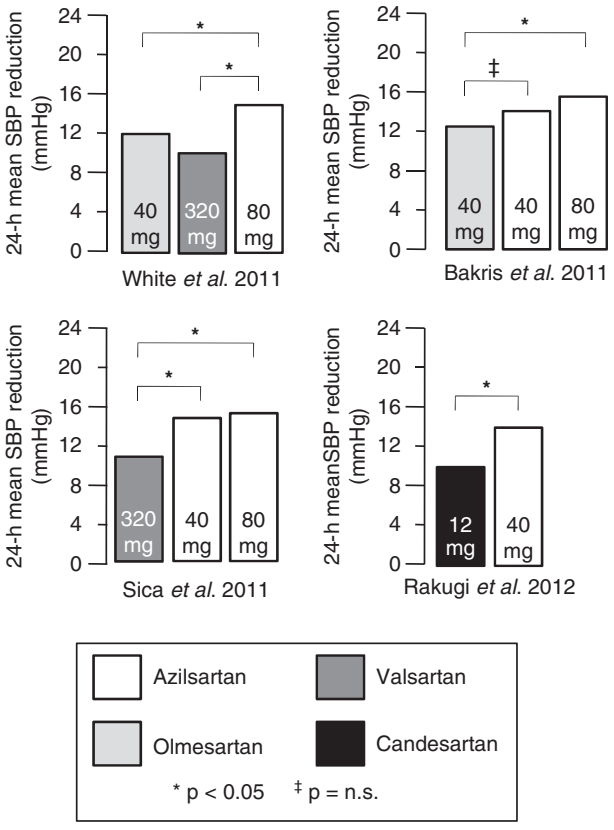


Figure 1. BP lowering effects of azilsartan compared with other ARBs. Absolute reductions from baseline in 24-h ambulatory systolic BP (mmHg) are depicted.
Data from [24-27].

medoxomil 40 and 80 mg (54.0 and 53.6%, respectively) than with ramipril 10 mg (33.8%; all $p < 0.001$). In addition, adverse events leading to discontinuation of treatment were less frequent with both doses of azilsartan compared with ramipril (2.4 and 3.1 vs 4.8%, respectively) [33].

In additional studies, when azilsartan was used in combination with either 25 mg of chlorthalidone or 5 mg of amlodipine [36,37], the combinations were shown to be more effective in lowering BP than with either chlorthalidone or amlodipine when used as monotherapies.

In a study comparing the combination of azilsartan plus chlorthalidone to the combination of olmesartan plus hydrochlorothiazide, the azilsartan/chlorthalidone combination was shown to be more effective in lowering both sitting and ambulatory BP [38].

Notably, azilsartan medoxomil is the only ARB that has been approved for use in a fixed dose combination with the diuretic chlorthalidone, whereas other ARBs are sold in fixed dose combinations with hydrochlorothiazide.

This deserves to be mentioned because of evidence suggesting that chlorthalidone seems to afford greater CV protection than hydrochlorothiazide [39].

5. Pleiotropic effects

Aside from blocking AT_1 receptors, some ARBs have been shown to provide additional benefits in CV protection [40,41]. In this regard, some preclinical studies have investigated possible pleiotropic effects of azilsartan in addition to BP control.

In particular, experimental studies investigated the effects of azilsartan on cardiac hypertrophy and fibrosis, atherosclerotic plaque, insulin resistance and renal function.

Kusumoto *et al.* [42] investigated the effect of azilsartan on insulin sensitivity. In this 2-week study in conscious spontaneously hypertensive rats, azilsartan medoxomil showed more stable antihypertensive effects than olmesartan medoxomil and improved the glucose infusion rate, an indicator of insulin sensitivity, more potently (≥ 10 times) than olmesartan medoxomil [42]. In addition, azilsartan medoxomil reduced urinary protein excretion more potently than olmesartan medoxomil [42].

It has been also suggested that azilsartan is capable of stabilizing atherosclerotic plaque and reducing cardiac fibrosis formation following myocardial infarction in mice; specifically, azilsartan medoxomil reduced the expression of plasminogen activator inhibitor type-I (PAI-1) in the aortic wall of transgenic mice which overexpressed PAI-1 in Vascular Smooth Muscle Cells (VSMCs) and was prone to atherosclerosis secondary to genetically determined apolipoprotein E deficiency [43].

Azilsartan medoxomil seems to also modulate other metabolic functions which can be involved in the atherosclerotic process. It has been shown to be superior in inhibiting the proliferation of rabbit aortic endothelial cells compared to valsartan [44], as it is indicated by the observation that it blocked the angiotensin II-induced activation of mitogen-activated protein kinases in vascular smooth muscle cells.

Taken together, these experimental observations seem to suggest that azilsartan could exert pleiotropic cardioprotective effects beyond the expected beneficial effects of the potent and sustained BP lowering action. However, specific studies in humans are required to support this hypothesis.

6. Safety and tolerability evaluation

Treatment with azilsartan is well tolerated, with an overall similar rate of adverse events as compared to placebo. In particular, it has been reported that treatment withdrawal due to adverse events ranged from 2 to 3% [11,45].

The most frequently occurring adverse event in patients receiving azilsartan was diarrhea 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 [11,14,45].

Other adverse events potentially related to treatment with azilsartan included nausea, asthenia, fatigue, muscle spasm, dizziness and cough. In clinical trials, the most common side effects included headache, dizziness, dyslipidemia and urinary tract infection [11,14,45].

Table 2. Monotherapy clinical trials which compared the efficacy of azilsartan with other ARBs in patients with hypertension.

Trial	Year of publication	Comparison	Treatment duration (weeks)
Rakugi *et al.* [25]	2012	Azilsartan/Candesartan	16
Bakris *et al.* [24]	2011	Azilsartan/Olmesartan/placebo	6
White *et al.* [27]	2011	Azilsartan/Olmesartan/Valsartan/placebo	6
Sica *et al.* [26]	2011	Azilsartan/Valsartan	24

Most of the changes in standard laboratory parameters were not clinically relevant.

A small and reversible increase in serum creatinine was observed with patients receiving azilsartan medoxomil 80 mg [14].

Low hemoglobin, hematocrit and red blood cell counts were observed only in 0.2, 0.4 and 0.3% of patients receiving azilsartan medoxomil, respectively [14].

7. Drug interactions

No significant drug interaction studies on azilsartan have been reported to date.

However, the manufacturer studied drug interactions with azilsartan and caffeine, tolbutamide, dextromethorphan, midazolam, fexofenadine, antiacid, digoxin, warfarin, glyburide, metformin, pioglitazone, chlorthalidone, amlodipine, fluconazole and ketoconazole.

Manufacturer reported that the pharmacokinetic profile of azilsartan was not significantly affected by these drugs [10].

Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors, may inhibit renal function when administered with azilsartan. This effect is reversible and is most likely to occur in elderly, volume-depleted or renally compromised patients.

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

8. Conclusion

Azilsartan medoxomil [7] is the eighth ARB approved for the management of patients with hypertension.

It is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and highly selective ARB with estimated bioavailability of 60% and elimination half-life of 12 h.

The effective therapeutic antihypertensive dosages of azilsartan medoxomil in humans vary from 40 to 80 mg/day.

Clinical trials have demonstrated that azilsartan is superior to alternative ARBs in lowering BP. In particular, available trials reported treatment with azilsartan 80 mg to have a statistically significant greater reduction in BP compared to valsartan, candesartan and olmesartan (**Table 2**) [24-27].

This response is due to its property of high affinity and slow dissociation to AT_1 receptors and its inverse agonistic properties. These characteristics attenuate angiotensin II-derived effects more persistently than other ARBs, leading to a prolonged functional effect [13,44].

Although the recommended oral dosage of azilsartan medoxomil is 80 mg/day 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. The use of azilsartan medoxomil 80 mg may result in symptomatic hypotension in that population [11]. Consequently, volume and salt depletion must be corrected before initiation of azilsartan medoxomil, and treatment should be started with a dose of 40 mg/day [11].

Although the improvement of clinical outcomes observed with the use of ARBs is largely mediated by their ability to decrease BP [46], azilsartan could exert pleiotropic cardioprotective effects beyond the expected beneficial effects of sustained BP-lowering action. Azilsartan seems to positively affect cardiac hypertrophy and fibrosis, atherosclerotic plaque formation and destabilization, insulin resistance and hypertensive renal damage. The results from these experimental studies are intriguing and make azilsartan an attractive candidate for further studies investigating clinical effects beyond simple BP control; however, replication in humans is required.

9. Expert opinion

High BP remains inadequately controlled in many hypertensive patients taking the available antihypertensive agents [47]. Therefore, it is often requisite to have a variety of therapeutic options in effectively controlling high BP. In this context, ARBs have been proven in many clinical studies to be effective in treating hypertension and its comorbid conditions and continuous efforts have been made in developing novel nonpeptide-AT_1 receptor blockers for the management of hypertensive disorders.

Following the introduction in the clinical arena of azilsartan medoxomil, eight ARBs are now available in Europe and United States for the treatment of hypertension.

Azilsartan is a new angiotensin II receptor antagonist indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents.

This agent has a unique pharmacological profile compared with other agents, demonstrating reduced AT_1 receptor dissociation rates and improved receptor specificity [11-13].

Studies indicate that azilsartan medoxomil 80 mg/day reduces BP to a greater extent than valsartan, candesartan and olmesartan, with a similar safety and tolerability profile.

The availability of a new ARB with greater ability to lower BP than 'older' ARBs could, nevertheless, be of clinical value.

However, two relevant aspects of the potential role of azilsartan in clinical practice need to be considered by clinicians. First, there is a lack of data supporting the use of azilsartan for improvement in long-term CV outcomes and reductions of CV mortality.

Second, clinical trials of azilsartan have been mainly conducted in patients without serious comorbidities. Whether azilsartan has distinctive advantages over other ARBs in the treatment of complicated hypertensive patients remains to be established.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties. No writing assistance was utilized in the production of this manuscript.

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