

Azilsartan/chlorthalidone combination therapy for blood pressure control

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Background: Edarbyclor[®] is a combined angiotensin receptor blocker (ARB) and thiazide-like diuretic (azilsartan and chlorthalidone), and was approved on December 20, 2011 by the US Food and Drug Administration (FDA) for hypertension management.

Objective: To review the pharmacology, pharmacokinetics, efficacy, safety, tolerability, and role of azilsartan plus chlorthalidone for hypertension management.

Methods: Peer-reviewed clinical trials, review articles, and relevant treatment guidelines, were identified from the databases MEDLINE and Current Contents (both 1966 to February 15, 2013, inclusive) using search terms “azilsartan”, “chlorthalidone”, “pharmacology”, “pharmacokinetics”, “pharmacodynamics”, “pharmacoeconomics”, and “cost-effectiveness”. The FDA website, as well as manufacturer prescribing information, was also reviewed to identify other relevant information.

Results: Azilsartan is a new ARB with high affinity for the angiotensin 1 receptor, approved by the FDA for hypertension management. Unlike other ARBs, azilsartan has no clinical data supporting improvement in cardiovascular outcomes, and is not approved for indications other than hypertension, which a select few other ARBs may be used for (eg, diabetic nephropathy and heart failure). Chlorthalidone is a longer acting thiazide-like diuretic that has been demonstrated to improve cardiovascular outcomes. Combination treatment with azilsartan/chlorthalidone is effective for reducing blood pressure. Compared to olmesartan/hydrochlorothiazide and azilsartan/hydrochlorothiazide combinations, azilsartan/chlorthalidone appears to be more efficacious for reducing blood pressure.

Conclusions: Azilsartan/chlorthalidone can be considered an antihypertensive therapy option in patients for whom combination therapy is required (blood pressure >20 mmHg systolic or >10 mmHg diastolic above goal). Cost to patients and insurance coverage will probably determine whether azilsartan/chlorthalidone will be the most appropriate combination therapy for an individual patient.

Keywords: azilsartan, chlorthalidone, hypertension

Introduction

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) defines hypertension as blood pressure (BP) greater than 140/90 mmHg in adults 18 years and older.¹ According to the National Health and Nutrition Examination Survey (NHANES) 2003–2006, 33.6% of Americans (74.5 million people) ≥ 20 years of age have hypertension.² Of these patients diagnosed with hypertension, 78% are aware of their diagnosis, 68% are taking antihypertensive medication, and despite knowledge gained from large clinical trials regarding hypertension management, only 44% of patients treated were well controlled. In 2010, it was estimated that the cost to manage hypertension in the US averaged near 76.6 billion in health care services, medications, and missed days of work.² Hypertension is a major risk factor

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for coronary heart disease, stroke, heart failure, and kidney disease.³ Thus, the ultimate goal for hypertension management is to reduce overall cardiovascular and renal morbidity and mortality.¹ This lack of medical success in optimally controlling BP is among one of the many reasons why new antihypertensive agents continue to be developed.

The current JNC7 guidelines recommend administering more than one drug as initial therapy for patients with BP >20 mmHg systolic or >10 mmHg diastolic above goal, with one of the drugs in the combination being a thiazide-type diuretic.¹ Treatment of hypertension with angiotensin receptor blockers (ARBs) alone or in combination is considered a first line therapy in patients without compelling indications as well as for those patients with specific compelling indications, including heart failure, diabetes, and post-myocardial infarction due to their cardiovascular morbidity and mortality benefits.¹ When using combination therapy, fixed-combination agents may have the potential to increase patient adherence.⁴ Many fixed-combination antihypertensive agents are available on the US market, and four of them are prescribed enough to be on the top 200 most prescribed drugs list in 2011.⁵ Azilsartan/chlorthalidone is unique in that it is the only combination drug that contains an ARB with the long-acting thiazide-like diuretic, chlorthalidone (instead of hydrochlorothiazide). It was approved on December 20, 2011 by the US Food and Drug Administration (FDA) for hypertension management. This article will discuss the clinical utility of fixed-combination azilsartan/chlorthalidone for the management of hypertension.

Methods

Peer-reviewed clinical trials, review articles, and relevant treatment guidelines, were identified from databases MEDLINE and Current Contents (both 1966 to February 15, 2013, inclusive) using search terms “azilsartan”, “chlorthalidone”, “pharmacology”, “pharmacokinetics”, “pharmacodynamics”, “pharmacoeconomics”, and “cost-effectiveness”. The FDA website as well as manufacturer prescribing information was also reviewed to identify other relevant information.^{9,19,25,26}

Results

Clinical pharmacology

Azilsartan

Mechanism of action

Azilsartan selectively blocks the binding of angiotensin (AT) II to the AT₁ receptors found in the vascular smooth muscle and the adrenal gland thereby promoting vasodilation and a decrease in the effects of aldosterone.^{6,7}

Azilsartan is structurally similar to candesartan. Both azilsartan and candesartan are highly selective antagonists for the AT₁ receptor compared to other ARBs, exhibiting a greater than 10,000-fold affinity for the AT₁ receptor compared to the AT₂ receptor.⁸ Azilsartan's antihypertensive effects are not diminished by increases in renin secretion due to its selective inhibition of the AT₁ receptor.⁷

Pharmacokinetics

A literature search did not reveal any pharmacokinetic studies on azilsartan published to date. However, based on materials submitted to the FDA, single and multiple dosing pharmacokinetics studies of azilsartan in the dose range of 20–320 mg have been conducted. No dosage adjustment of azilsartan is warranted based on a patient's age, gender, race, or degree of renal/hepatic impairment.

Azilsartan medoxomil is a prodrug that is hydrolyzed to its active moiety, azilsartan, in the gastrointestinal tract. Peak plasma concentrations of azilsartan are reached in 1.5–3 hours following oral administration. Coadministration with food does not affect the bioavailability of azilsartan. The absolute bioavailability of azilsartan is approximately 58%.⁷ The volume of distribution of azilsartan is estimated to be 30 L in healthy subjects. Azilsartan is greater than 99% bound to plasma proteins and is concentration independent.⁷ Azilsartan is metabolized in the liver via cytochrome P450 (CYP) 2C9 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). Systemic exposure to M-II and M-I was approximately 50% and less than 1% of azilsartan, respectively. Azilsartan does not inhibit or induce the CYP system. However, azilsartan medoximil (the prodrug), and not azilsartan, is an inhibitor of the efflux transporter, p-glycoprotein. Azilsartan is primarily excreted in the urine as inactive metabolites. The renal clearance of azilsartan is 2.3 mL/minute. Based on radiolabeled animal studies in which a C14 radiolabeled dose of azilsartan was given via the oral route, approximately 97% of the administered dose was recovered in 14 days, of which 42% was recovered in urine (15% of the dose excreted as azilsartan) and 55% in feces. The elimination half-life of azilsartan is approximately 11 hours, with steady-state plasma concentrations reached by day five after oral administration.⁷

Drug interactions

A literature search did not reveal any drug interaction studies on azilsartan published to date. Azilsartan is

metabolized by CYP2C9. Based on data submitted to the FDA, drug interactions have been studied with azilsartan and caffeine, antacid, warfarin, digoxin, tolbutamide, glyburide, metformin, pioglitazone, chlorthalidone, amlodipine, dextromethorphan, midazolam, and fexofenadine. No significant interactions were observed between these agents and azilsartan.

In another drug interaction study of 36 healthy volunteers with an average age of 30 years, subjects were given azilsartan 40 mg daily for 1 day, fluconazole 200 mg daily or ketoconazole 400 mg daily for 5 days, and azilsartan 40 mg plus fluconazole 200 mg daily or ketoconazole 400 mg for 1-day for three consecutive periods with a 3-day washout inbetween. Clearance of azilsartan was reduced when coadministered with fluconazole (CYP2C9 inhibitor) with an increase in area under the curve by ~40%. When coadministered with ketoconazole (a CYP3A4/5 inhibitor), the area under the curve of azilsartan was decreased by approximately 20%. The clinical significance of this interaction was not examined.

Although not specifically evaluated, the manufacturer Novartis (East Hanover, NJ, USA) has issued a warning in their prescribing information cautioning the use of azilsartan with non-steroidal anti-inflammatory agents and COX-2 inhibitors.⁷ Angiotensin II increases the glomerular filtration rate by causing constriction of the efferent arteriole. Decreased angiotensin II binding to the receptor with azilsartan use decreases the glomerular filtration rate because of dilatation of the efferent arteriole. Non-steroidal anti-inflammatory agents and COX-2 inhibitors cause pre-renal acute renal failure by blocking prostaglandin production, which also alters local glomerular arteriolar perfusion.⁹ Concurrent use of these agents may result in additive risk in deterioration of renal function.

Compared to other ARBs

The antihypertensive effects of azilsartan has been compared to olmesartan and valsartan. The effect of azilsartan on cardiovascular events/outcomes has not been studied.

Bakris et al performed a randomized, placebo-controlled study, comparing the antihypertensive efficacy and safety of azilsartan, olmesartan, and placebo.¹⁰ One thousand two hundred and seventy-five patients aged over 18 years of age, with primary hypertension (systolic blood pressure [SBP] between 150–180 mmHg) were randomized to placebo, or azilsartan 20 mg, 40 mg, or 80 mg daily, or olmesartan 40 mg daily for 6 weeks. Dose-dependent reductions in 24-hour mean SBP (measured by 24 hours ambulatory

blood pressure monitoring [ABPM]) at study end occurred in all azilsartan groups (20 mg, -12.2 mmHg; 40 mg, -13.5 mmHg; 80 mg, -14.6 mmHg) and olmesartan 40 mg group (-12.6 mmHg), $P < 0.05$ for all. Reduction in 24-hour mean SBP was greater with azilsartan 80 mg than olmesartan 40 mg by 2.1 mmHg (95% confidence interval [CI] -4.0 to -0.1; $P = 0.038$), while azilsartan 40 mg was not inferior to olmesartan 40 mg. The side effect profiles of both angiotensin receptor blockers were similar to placebo (not statistically compared). The study demonstrated that azilsartan is well tolerated and more efficacious at its maximal dose than the highest recommended dose of olmesartan in this 6-week study.

White et al performed a double-blind, randomized, placebo-controlled trial comparing the antihypertensive efficacy and safety of azilsartan, olmesartan, valsartan, and placebo.¹¹ One thousand two hundred and eighty-five patients aged over 18 years of age with primary hypertension (SBP between 150–180 mmHg) were randomized to placebo, or azilsartan 40–80 mg daily, olmesartan 40 mg daily, or valsartan 320 mg daily for 6 weeks. The mean age of participants was 56 years. Azilsartan at 80 mg had superior efficacy to both valsartan at 320 mg and olmesartan at 40 mg: placebo-adjusted 24-hour SBP (measured by ABPM) was lowered (-14.3 mmHg) more than 320 mg of valsartan (-10.0 mmHg; $P < 0.001$ azilsartan versus valsartan) and 40 mg of olmesartan (-11.7 mmHg; $P < 0.009$ azilsartan versus olmesartan). Azilsartan at 40 mg was not inferior to 40 mg of olmesartan (difference: -1.4 mmHg [95% CI: -3.3 to 0.5]). Safety and tolerability were similar among the placebo and four active treatments (not statistically compared). This study demonstrated that azilsartan at its maximum dose is more efficacious than both olmesartan and valsartan at their maximum approved doses without increasing adverse events.

Sica et al performed a double-blind, randomized trial comparing the antihypertensive efficacy and safety of azilsartan and valsartan.¹² Nine hundred and eighty-four patients aged over 18 years of age with primary hypertension (SBP between 150–180 mmHg) were randomized to placebo, or azilsartan 20 mg titrated to 40 mg, 40 mg titrated to 80 mg daily, or valsartan 80 mg titrated to 320 mg for 24 weeks. The mean age of participants was 58 years. Azilsartan 40 mg and 80 mg lowered 24-hour mean SBP (-14.9 mmHg and -15.3 mmHg, respectively) more than valsartan 320 mg (-11.3 mmHg; $P < 0.001$ for 40 mg and 80 mg comparisons versus valsartan). This study demonstrated that azilsartan across the effective dose range is more effective than

valsartan at its maximum recommended dose for lowering BP with a similar adverse event profile.

Chlorthalidone

Mechanism of action

Though commonly considered a thiazide, unlike hydrochlorothiazide, chlorthalidone is not a benzothiadiazine and is more appropriately called a thiazide-like diuretic.¹³ Although structurally different, chlorthalidone and thiazide diuretics appear to produce their diuretic effect by direct effect on the distal convoluted tubule of the nephron, resulting in decreased extracellular fluid volume, plasma volume, and total exchangeable sodium. It is postulated that sodium and water depletion provide a basis for its antihypertensive effect.

Pharmacokinetics

Chlorthalidone is 100% absorbed with serum concentrations peak at approximately 2–6 hours after oral administration.^{14,15} One randomized, crossover study in healthy volunteers found that peak serum concentrations after single doses of 50 mg, 100 mg, or 200 mg were 3.2 µg/mL, 5.6 µg/mL, and 7.9 µg/mL, respectively.¹⁴ The half-life of chlorthalidone in this single-dose study was approximately 42 hours (range, 29–55 hours, longer than hydrochlorothiazide, which ranged from 6–9 hours). Interindividual variability in the half-life of chlorthalidone is large, with typical mean half-lives of 45 to 60 hours after long-term dosing.^{14,15} Chlorthalidone serum concentrations after 100 mg are only twice those of a 25 mg dose, indicating a flat dose-serum concentration curve.¹⁴ Chlorthalidone rapidly enters (half-life, 15 minutes) and concentrates in erythrocytes.¹⁶ Studies have found 7 to 10 times greater concentrations of chlorthalidone in erythrocytes than in plasma.^{14,15} One possible explanation for the long half-life is that chlorthalidone concentrates in erythrocytes and is slowly released from this compartment. The natriuretic effect of chlorthalidone was maximal at 18 hours and lasted greater than 48 hours. Although the half-life of chlorthalidone is relatively long, one double-blind study found that three times weekly dosing of chlorthalidone did not completely control SBP, suggesting that every-other-day dosing might not be maximally effective.¹⁷ The major portion of the drug is excreted unchanged by the kidneys. Nonrenal routes of elimination have yet to be clarified. Data are not available regarding percentage of dose as unchanged drug and metabolites, concentration of the drug in body fluids, degree of uptake by a particular organ or in the fetus, or passage across the blood–brain barrier.¹⁸

Drug interactions

No significant direct drug interactions with chlorthalidone have been reported. If chlorthalidone causes significant hypokalemia, the risk of arrhythmia may increase when used with other medications that have the risk to prolong QT interval. Lithium renal clearance is reduced by diuretics, such as chlorthalidone, increasing the risk of lithium toxicity.¹⁸

Compared to thiazides

The antihypertensive effects of chlorthalidone and hydrochlorothiazide have been compared.¹³ The earliest study of dose equivalence was a randomized, double-blind study of placebo, hydrochlorothiazide 100 mg daily, and chlorthalidone 50 mg daily, each given for 6 weeks separated by a 2-week washout. Pretreatment BPs were $\leq 180/110$ mmHg. Chlorthalidone 50 mg reduced BP by 25/10 mmHg, and hydrochlorothiazide 100 mg reduced BP by 18/8 mmHg (no significant difference between the two agents). Another double-blind, randomized study evaluated of hydrochlorothiazide 50 mg twice daily (100 mg daily) compared to chlorthalidone 50 mg daily. After 4 weeks of treatment, chlorthalidone reduced mean BP by 18/15 mmHg, whereas hydrochlorothiazide reduced mean BP by 22/16 mmHg (no significant difference between drugs). The percentage of patients with diastolic BP < 90 mmHg was 42% with chlorthalidone and 32% with hydrochlorothiazide.

Although no prospective, randomized trials assessing cardiovascular outcomes between chlorthalidone and hydrochlorothiazide have been conducted, evidence indicates that chlorthalidone may be superior to hydrochlorothiazide.¹⁹ The Multiple Risk Factor Intervention Trial (MRFIT) was first to propose a clinical benefit with chlorthalidone compared to hydrochlorothiazide.¹⁹ MRFIT was a large randomized primary prevention trial assessing the efficacy of a multifactor intervention program, which included dietary advice, smoking cessation counseling, and hypertension treatment, compared to usual care. Patients in the study could receive chlorthalidone or hydrochlorothiazide for hypertensive therapy. Approximately 5 years after randomization, the diuretic treatment protocol was changed to replace treatment with hydrochlorothiazide to chlorthalidone due to a 44.1% higher coronary heart disease mortality in clinics predominantly prescribing hydrochlorothiazide compared to the usual care group ($P = 0.23$), whereas the clinics predominantly prescribing chlorthalidone had a –58.2% (reduction) in coronary heart disease mortality compared to usual care. After the change was instituted, the

rate of coronary heart disease mortality in the previously predominant hydrochlorothiazide clinics decreased to -7.9% when compared to usual care. A subsequent retrospective cohort analysis of the data from MRFIT demonstrated that cardiovascular events were significantly lower in those on chlorthalidone (adjusted hazard ratio 0.51 [95% CI 0.43–0.62], $P < 0.0001$) and on hydrochlorothiazide (adjusted hazard ratio 0.65 [95% CI 0.55–0.75], $P < 0.0001$) compared to those who took neither drug. When comparing the two drugs, chlorthalidone had significantly fewer cardiovascular events compared to hydrochlorothiazide ($P = 0.0016$). Patients receiving chlorthalidone also had significantly lower SBP ($P < 0.0001$), lower low-density lipoprotein ($P = 0.0009$), lower potassium ($P = 0.0003$), and higher uric acid ($P < 0.0001$) over time compared to hydrochlorothiazide.²⁰

Clinical trials

Azilsartan plus chlorthalidone combination has been evaluated for hypertension management. A dose response study, a study comparing the efficacy of azilsartan plus chlorthalidone and azilsartan plus hydrochlorothiazide, and a study comparing the efficacy of azilsartan plus chlorthalidone and olmesartan plus hydrochlorothiazide have been published in the literature to date.^{21–23} In addition, based on materials submitted to the FDA, two other efficacy studies have also been performed (Table 1).²³ The studies evaluating the efficacy of azilsartan plus chlorthalidone for management of hypertension will be reviewed below.

Sica et al performed a study comparing the efficacy and safety of fixed-dose combinations of the azilsartan and chlorthalidone with the individual monotherapies in a double-blind factorial study.²¹ A total of 1714 patients age >18 years, with SBP 160 mmHg to 190 mmHg inclusive were randomized to azilsartan 0 mg, 20 mg, 40 mg, or 80 mg and /or chlorthalidone 0 mg, 12.5 mg, or 25 mg. The primary efficacy end point was change of mean SBP (measured by 24 hour ABPM) from baseline to 8 weeks. Baseline BP was an averaged 165/95 mmHg. For the pooled azilsartan/chlorthalidone 40/25 mg and 80/25 mg fixed dose combination groups, SBP reduction was 28.9 mmHg (similar between 40/25 mg and 80/25 mg) and exceeded azilsartan 80 mg and chlorthalidone 25 mg monotherapies by 13.8 mmHg and 13 mmHg, respectively ($P < 0.001$ for both comparisons). Each of the six individual azilsartan/chlorthalidone doses led to significantly greater reductions in SBP compared to their respective azilsartan and chlorthalidone components. Treatment with azilsartan/

chlorthalidone resulted in a similar magnitude of BP reduction in African American patients compared with the overall population, even though African American patients have been previously demonstrated to be less responsive to azilsartan alone.²⁴ Discontinuation rates and elevations in serum creatinine were dose-dependent and occurred more often in the combination azilsartan/chlorthalidone groups (0.6%–5% compared to $<1\%$ in monotherapy groups). In patients with stage two hypertension, the investigators concluded that, as expected, treatment with the combination of azilsartan and chlorthalidone resulted in substantially greater SBP reduction compared with either agent alone.

Cushman et al compared the efficacy of once-daily fixed-dose combinations of azilsartan/chlorthalidone force titrated to a high dose of either 40/25 mg or 80/25 mg with a fixed-dose combination of the olmesartan/hydrochlorothiazide force titrated to 40/25 mg.²² One thousand and seventy-one subjects aged >18 years, with baseline SBP between 160 to 190 mmHg and diastolic BP ≤ 119 mmHg were randomized. The primary efficacy end point was change of mean SBP (measured by 24 hours ABPM) from baseline to 12 weeks. Changes in SBP at week 12 were significantly greater in both azilsartan/chlorthalidone arms than in the olmesartan/hydrochlorothiazide arm (42.5 mmHg, 44.5 mmHg and 37.1 mmHg respectively, $P < 0.001$ for all comparisons). Adverse events leading to permanent drug discontinuation occurred in 7.9%, 14.5%, and 7.1% of the groups given azilsartan/chlorthalidone 40/25 mg, azilsartan/chlorthalidone 80/25 mg, and olmesartan/hydrochlorothiazide 40/25 mg, respectively. The investigators concluded that azilsartan/chlorthalidone combination was more effective in reducing BP than olmesartan/hydrochlorothiazide combination. It is, however, important to note that the approximate equivalent dose of chlorthalidone 25 mg is hydrochlorothiazide 50 mg. Therefore, it is possible that the unequal potency doses were being compared.

Bakris et al compared the efficacy of azilsartan/chlorthalidone combination and azilsartan/hydrochlorothiazide combination.²³ Six hundreds and nine patients aged >18 years with stage 2 primary hypertension were randomized to receive 12.5 mg of chlorthalidone or hydrochlorothiazide in addition to azilsartan for 4 weeks, and titrated up to 25 mg for another 4 weeks if BP was not controlled, after receiving azilsartan 40 mg alone for 2 weeks. Target BP was defined as clinical BP $<140/90$ mmHg for participants without diabetes or chronic kidney disease and $<130/80$ mmHg for participants with diabetes or chronic kidney disease.

Table 1 Pertinent clinical studies of azilsartan/chlorthalidone in hypertension management

Study	Design	Population	Treatment (all doses once daily)	Efficacy	Most common adverse events of AZ/Chlor
Sica et al ²¹	Double-blind factorial study	N = 1714 Average age: 57 SBP 160–190 mmHg	AZ 0, 20, 40, 80 mg and/or Chlor 0, 12.5, 25 mg	Reduction in mean SBP (measured by 24 hours ABPM) in 8 weeks AZ(mg)/Chlor(mg) 0 12.5 -21.2 mmHg [#] 0 25 -27.1 mmHg ^{#,Ω} 20 0 -19.8 mmHg 20 12.5 -33.8 mmHg ^{#,Ω} 20 25 -37 mmHg ^{#,Ω} 40 0 -23.3 mmHg 40 12.5 -36.8 mmHg ^{#,Ω} 40 25 -39.6 mmHg ^{#,Ω} 80 0 -24.2 mmHg 80 12.5 -36.9 mmHg ^{#,Ω} 80 25 -40.1 mmHg ^{#,Ω}	Serum creatinine increase (0.6%–5%), dizziness (1.3%–13.5%), headache (0.7%–12.2%), increase uric acid (2.7%–32.9%)
Cushman et al ²²	Double-blind, randomized	N = 1071 Average age: 57 SBP 160–190 mmHg	AZ/Chlor 40/25 mg AZ/Chlor 80/25 mg Olm/HCTZ 40/25	Reduction in mean SBP (measured by 24 hours ABPM) in 12 weeks AZ/Chlor 40/25 mg: -42.5 mmHg [^] AZ/Chlor 80/25 mg: -44.5 mmHg [^] Olm/HCTZ 40/25 mg: -37.1 mmHg	Increase in serum creatinine: 18.6%–22.2% Dizziness: 11.5%–16.5% Increase in uric acid: 4.8%–5.4%
Bakris et al ²³	Double-blind, randomized	N = 609 Average age: 56.4 SBP 160–190 mmHg	AZ 40 mg + Chlor or HCTZ 12.5–25 mg	Reduction of clinic SBP in 6 weeks AZ/Chlor: -31.5 mmHg [*] AZ/HCTZ: -29.5 mmHg	Dizziness: 12.3% Increase in serum creatinine: 12.9% Headache: 5.3%
491-CLD-301 ²⁴	Double-blind, randomized	N = 1085 Age >18 years SBP 160–190 mmHg	AZ/Chlor 40/25 mg AZ/Chlor 80/25 mg Olm/HCTZ 40/25	Reduction of clinic SBP in 12 weeks AZ/Chlor 40/25 mg: -38 mmHg [^] AZ/Chlor 80/25 mg: -38 mmHg [^] Olm/HCTZ 40/25 mg: -32 mmHg	Increase in serum creatinine (2.5%), fatigue (3.8%), hypotension (1.1%).
01-05-TL-491-009 ²⁴	Double-blind, randomized, controlled	N = 551 Average age: 58 SBP 160–190 mmHg	Chlor 25 mg AZ 40 mg + Chlor 25 mg AZ 80 mg + Chlor 25 mg 6 weeks	Compared to placebo (mean SBP [measured by 24 hours ABPM] change): Chlor 25 mg: -16 mmHg AZ 40 mg + Chlor 25 mg: -31.75 mmHg [#] AZ 80 mg + Chlor 25 mg: -31.3 mmHg [#]	More common side effect of AZ: hypotension (5 patients), dizziness (4 patients) Increase in creatinine: AZ 40 mg: 7.7%, 80 mg: 7.9%, Chlor monotherapy: 2.2%

Notes: [#]*P* < 0.05 compared to azilsartan/HCTZ; [^]*P* < 0.05 compared to olmesartan/HCTZ; ^{*}*P* < 0.05 compared to chlorthalidone alone; ^Ω*P* < 0.05 compared to azilsartan alone.

Abbreviations: ABPM, ambulatory blood pressure monitoring; AZ, azilsartan; Chlor, chlorthalidone; Olm, olmesartan; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure.

Azilsartan/chlorthalidone combinations provided greater reduction in SBP than azilsartan/hydrochlorothiazide combinations (31.5 mmHg versus 29.5 mmHg, *P* < 0.001). The percentage of participants achieving target BP at week 6 was greater for the chlorthalidone versus hydrochlorothiazide combination (64.1% versus 45.9%, *P* < 0.001). Drug discontinuations due to adverse events were not statistically significantly different between groups (9.3% versus 7.3%, *P* = 0.38), and hypokalemia was uncommon in both groups. The investigators concluded that chlorthalidone combined with azilsartan provides better BP control than

hydrochlorothiazide combined with azilsartan. Similar to the Cushman et al study discussed above, it is important to note that the approximate equivalent dose of chlorthalidone 25 mg is hydrochlorothiazide 50 mg. Therefore, it is possible that the unequal potency doses were being compared.

Study 491-CLD-301 compared the efficacy of once-daily fixed-dose combinations of azilsartan/chlorthalidone of 20/12.5 mg, or 40/25 mg with a fixed-dose combination and olmesartan/hydrochlorothiazide 20/12.5 mg.²⁵ One thousand and eighty-five subjects aged >18 years, with baseline SBP between 160 to 190 mmHg and diastolic BP ≤119 mmHg

were randomized. If subjects achieved both target SBP and diastolic BP (<140/90 mmHg for subjects without diabetes or chronic kidney diseases or <130/80 mmHg for subjects with diabetes or chronic kidney disease) by the end of Week 4, they continued to receive their starting dose for the duration of the study. For subjects who did not achieve both target SBP and diastolic BP by Week 4, study drug was titrated to azilsartan/chlorthalidone 40/25 mg, 80/25 mg, and olmesartan/hydrochlorothiazide 40/25 mg. The primary endpoint was the change from baseline to Week 8 in SBP. SBP reductions at week 8 in both azilsartan/chlorthalidone treatment groups (33 to 38 mmHg) were significantly ($P < 0.05$) greater than in the olmesartan/hydrochlorothiazide group (27 to 32 mmHg). Approximately 13% of subjects prematurely discontinued the study, including 15% and 14% in the azilsartan/chlorthalidone low-dose and high-dose groups, respectively, and 9% in the olmesartan/hydrochlorothiazide group. The most common side effects in the azilsartan/chlorthalidone group included serum creatinine elevation (2.5% in the high dose group), fatigue (3.8% in the high dose group), and hypotension (1.1% in the high dose group). It is again important to note that the approximate equivalent dose of chlorthalidone 25 mg is hydrochlorothiazide 50 mg. Therefore, it is possible that the unequal potency doses were being compared.

Study 01-05-TL-491-009 is a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of azilsartan when coadministered with chlorthalidone.²⁵ Five hundred and fifty-one subjects with SBP 160–190 mmHg and aged >18 years were randomized to received placebo plus chlorthalidone 25 mg daily, azilsartan 40 mg daily plus chlorthalidone 25 mg daily, or azilsartan 80 mg plus chlorthalidone 25 mg daily for 6 weeks. At the end of the treatment period, chlorthalidone alone decreased mean SBP (measured by 24 hours ABPM) by 16 mmHg. There was no differences between the two azilsartan and chlorthalidone groups (40 mg, -31.72 mmHg; 80 mg, -31.3 mmHg; $P > 0.05$) but both groups compared to chlorthalidone alone significantly reduced SBP ($P < 0.05$ for both). Adverse events of hypotension (five patients), dizziness (four patients), and asthenia (one patient) were reported in the azilsartan groups. However, the increases in serum creatinine ($\geq 30\%$ from baseline) from baseline in the azilsartan 40 mg and 80 mg combination groups were more than double the increases reported in the chlorthalidone monotherapy group (increase in creatinine-azilsartan 40 mg, 28 patients (7.7%), and 80 mg, 41 patients (7.9%); chlorthalidone monotherapy: 4 patients (2.2%), P -value not reported). This study demonstrated that azilsartan, when used with chlorthalidone, produced a further

reduction in BP. However, creatinine needs to be monitored for potential worsening of renal function.

Overall, azilsartan/chlorthalidone has demonstrated the ability to lower BP in numerous randomized, double blind, placebo controlled trials. It appears that there is little difference in BP lowering effect among the azilsartan doses of 40 and 80 mg. The BP lowering effect appeared to be superior to olmesartan and hydrochlorothiazide.

Adverse events

According to the manufacturer (Novartis), a total of 3900 patients were evaluated in premarketing clinical trials for safety when treated with azilsartan/chlorthalidone for 6 months to 1-year.¹⁸ Azilsartan/chlorthalidone was generally well tolerated and adverse reactions have generally been mild and transient in nature. Common adverse reactions that occurred in the 8-week factorial design trial included dizziness (8.9%) and fatigue (2%).¹⁸ Hypotension and syncope were reported in 1.7% and 0.3%, respectively, of patients treated with azilsartan/chlorthalidone. Study discontinuation because of adverse reactions occurred in 8.3% of patients treated with the recommended doses of azilsartan/chlorthalidone combination compared to 3.2% of patients treated with azilsartan and 3.2% of patients treated with chlorthalidone. The most common reasons for discontinuation of therapy with azilsartan/chlorthalidone were serum creatinine increase (3.6%) and dizziness (2.3%). The adverse reaction profile obtained from 52 weeks of open-label combination therapy with azilsartan plus chlorthalidone was similar to that observed during the double-blind, active controlled trials, with an overall incidence of adverse reactions similar to placebo. Increased serum creatinine is a known pharmacologic effect of renin-angiotensin aldosterone system blockers, such as ARBs and angiotensin converting enzyme (ACE) inhibitors, and is related to the magnitude of BP reduction. The incidence of consecutive increases of creatinine $\geq 50\%$ from baseline was 2.0% in patients treated with the recommended doses of azilsartan/chlorthalidone compared to 0.4% and 0.3% with azilsartan and chlorthalidone alone, respectively. Elevations of creatinine were typically transient, or nonprogressive and reversible. Mean increases in blood urea nitrogen were observed with azilsartan/chlorthalidone (5.3 mg/dL) compared to azilsartan (1.5 mg/dL) and with chlorthalidone (2.5 mg/dL).

Contraindications/precautions

According to the manufacturer (Novartis), azilsartan/chlorthalidone is contraindicated in patients with anuria.¹⁸

The manufacturer cautions against the use of azilsartan/chlorthalidone in pregnant woman, as drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women during the second and the third trimester.¹⁸ Azilsartan/chlorthalidone is pregnancy category D.¹⁸ In addition, patients who are volume- or salt-depleted may be more sensitive to the hypotension effect of azilsartan. In patients whose renal function may depend on the activity of the renin-angiotensin system (including severe congestive heart failure, renal artery stenosis, or volume depletion), treatment with ACE inhibitors and ARBs has been associated with oliguria or progressive azotemia. Hypokalemia is a dose-dependent adverse reaction that may develop with chlorthalidone. Coadministration of digitalis may exacerbate the adverse effects of hypokalemia. Azilsartan may attenuate chlorthalidone-associated hypokalemia. Hyperuricemia may occur or gout may be precipitated in some patients receiving chlorthalidone or thiazide diuretics.

Dosage and administration

The recommended starting dose of azilsartan/chlorthalidone is 40/12.5 mg taken orally once daily. Most of the antihypertensive effect is apparent within 1 to 2 weeks. The dosage may be increased to 40/25 mg after 2 to 4 weeks as needed to achieve BP goals. Azilsartan/chlorthalidone doses above 40/25 mg probably do not provide significant additional antihypertensive effects.

Pharmacoeconomics/cost-effectiveness

A literature search reviewed no formal cost-effectiveness study performed for azilsartan to date. The average wholesale price of azilsartan/chlorthalidone in the US is \$109.60 for a 30-day supply for both the 40/12.5 mg and the 40/25 mg tablets.²⁶ In terms of acquisition cost, azilsartan/chlorthalidone is less expensive than other ARB/thiazide combinations on the market (Table 2).

Discussion/future perspective

Clinical studies to date demonstrated that the azilsartan/chlorthalidone combination is effective in lowering BP and more effective than either single agent alone. Its antihypertensive effect also appears to be better than the olmesartan/hydrochlorothiazide combination. Medications that have direct effects on the renin-angiotensin aldosterone system, such as ACE inhibitors, ARBs, and aldosterone antagonists have been found to not only be effective in lowering BP, but also improve mortality and morbidity

Table 2 Comparative cost (average wholesale price) of angiotensin receptor blocker-diuretic combination used in the United States²⁴

Antihypertensives	Cost for 30-day supply (US\$)
Azilsartan/chlorthalidone tablet	
40–12.5 mg	109.60
40–25 mg	109.60
Candesartan/hydrochlorothiazide tablet	
16–12.5 mg	368.18
32–12.5 mg	375.51
32–25 mg	406.48
Olmesartan/hydrochlorothiazide tablet	
20–12.5 mg	119.88
40–12.5 mg	167.04
40–25 mg	501.12
Valsartan/hydrochlorothiazide tablet	
80–12.5 mg	117.99
160–12.5 mg	128.37
160–25 mg	145.58
320–12.5 mg	162.44
320–25 mg	184.29
Losartan/hydrochlorothiazide tablet	
50–12.5 mg	75.05
100–25 mg	102.23
Telmisartan/hydrochlorothiazide tablet	
40–12.5 mg	133.96
80–25 mg	133.96
Eprosartan/hydrochlorothiazide tablet	
600–12.5 mg	488.15
600–25 mg	488.15

in patients with heart failure (ACE inhibitors, ARBs, and aldosterone antagonists), history of myocardial infarction (ACE inhibitors, ARBs, and aldosterone antagonists), and nephropathy (ACE inhibitors and ARBs). Whether azilsartan will be as effective of other ARBs (valsartan, candesartan, irbesartan) is not known. A literature review did not identify any published studies performed evaluating the effect of azilsartan on long-term vascular outcomes. Further research investigating these potential roles will help establish a place for azilsartan in cardiovascular disease management, in addition to hypertension treatment. Chlorthalidone has been demonstrated to improve cardiovascular outcomes.

The current JNC7 guidelines recommend administering more than one drug as initial antihypertensive therapy for patients with BP >20 mmHg systolic or >10 mmHg diastolic above goal, with one of these drugs being a thiazide and thiazide-like diuretic.¹ As seen in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), 63% of the study population was eventually on two or more antihypertensive agents and at

the end of 5 years only 66% had achieved controlled BP.²⁸ Numerous newer trials have also shown high rates of patients requiring more than one drug for BP management, such as International Verapamil SR trandolapril Study (INVEST) (80%), Anglo-Scandinavian Cardiac Outcomes Trial: Blood Pressure-Lowering Limb (ASCOT-BPLA) (78%), and Losartan Intervention For Endpoint (LIFE) (88%).^{28–30} Since a large number of hypertensive patients require more than one drug to control their hypertension, many trials have examined the benefit of combinations of antihypertensive medications as well as the benefit of combination therapy as initial treatment. The prompt achievement of BP goal may also be a benefit of initial combination therapy opposed to initial monotherapy later progressing to combination therapy. Results from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, comparing a valsartan-based BP regimen to an amlodipine-based BP regimen, suggest that obtaining BP control within the first month of treatment is correlated to a lower rate of cardiovascular events.³¹ A large, case-control study showed an 11% decrease in cardiovascular events when patients receiving antihypertensive medications were initiated on combination therapy instead of monotherapy (odds ratio OR 0.74; 95% CI: 0.65–0.85).³² These data suggest that the best outcomes may be achieved when combination therapy is initially started in hypertensive patients. The combination of azilsartan/chlorthalidone has not been tested in specific study designs.

Currently, azilsartan/chlorthalidone can be considered an alternative antihypertensive regimen for patients who require combination therapy. Serum creatinine needs to be monitored when patients are receiving combination therapy as it has been demonstrated in clinical studies that the incidence of elevation of serum creatinine in combination therapy is higher than using individual agents alone.

Conclusion

Azilsartan is a new ARB with high affinity to the AT₁ receptor that is approved by the FDA for hypertension management. Unlike other ARBs, azilsartan has no clinical data supporting improvement of cardiovascular outcomes, and is not approved for indications which selected other ARBs may be used for (eg, diabetic nephropathy and heart failure). Chlorthalidone is a longer acting thiazide like diuretic that has been demonstrated to improve cardiovascular outcomes. Compared to olmesartan/hydrochlorothiazide and azilsartan/hydrochlorothiazide combinations, azilsartan/chlorthalidone appears to be more efficacious in reducing BP. Azilsartan/chlorthalidone can be considered as an antihypertensive therapy

option in patients whom combination therapy is required (BP >20 mmHg systolic or >10 mmHg diastolic above goal). Cost to patients and insurance coverage will probably determine whether azilsartan/chlorthalidone would be the most appropriate combination therapy for an individual patient.

Disclosure

The author declares no conflicts of interest in this work.

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