EXPERT REVIEWS

Efficacy of azilsartan medoxomil with chlorthalidone in hypertension

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Azilsartan medoxomil (AZL) is the most recently approved angiotensin receptor blocker (ARB) for treating patients with hypertension. A fixed-dose combination product with AZL and the thiazide-like diuretic chlorthalidone (CLD) is now available to treat individuals who require additional blood pressure lowering. For this review, a literature search was conducted using MEDLINE and the keywords and MeSH terms azilsartan, azilsartan medoxomil, chlorthalidone, thiazide, blood pressure and hypertension. References for retrieved articles were also scanned for relevant citations. No language restrictions were used. AZL is structurally related to candesartan and has been shown to provide more potent angiotensin receptor antagonism versus other ARBs. CLD is a thiazide-like diuretic with a longer half-life and greater blood pressure lowering efficacy than hydrochlorothiazide. The combination of AZL plus CLD has superior efficacy to other ARBs alone or in combination with hydrochlorothiazide based on extensive evaluation in clinical trials. This superior efficacy is not offset by a large imbalance in clinically important adverse events.

Keywords: angiotensin receptor blocker • azilsartan medoxomil • chlorthalidone • combination • hypertension

Attainment and maintenance of blood pressure (BP) control is critical to the successful management of hypertension [1–3]. A majority of patients will require at least two antihypertensives to reach desired BP goals [3]. Current treatment approaches endorse initiation of dual antihypertensive therapy for patients who are unable to reach BP targets with monotherapy alone and/or those who are >20 mmHg above systolic or >10 mmHg above diastolic goals [1–3]. Preferred treatment regimens include thiazide-like diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs) [1–3]. Combining antihypertensives with synergistic mechanisms of action is likely to lead to greater reductions in BP when compared with doubling the dose of a single medication [4]. Additionally, when fixed-dose combinations are used, medication adherence to antihypertensive therapy may be enhanced [5,6].

Azilsartan medoxomil (AZL)/chlorthalidone (CLD) is a newly approved potent combination therapy for hypertension. Currently, it is the only combination to contain an ARB and a long-acting thiazide-like diuretic. In this article, we evaluate relevant data and provide clinical considerations for the role of azilsartan/CLD for the treatment of hypertension.

Pharmacological properties of AZL

AZL is a prodrug that is hydrolyzed within the gastrointestinal tract to azilsartan prior to and/or during absorption. Azilsartan is structurally related to candesartan with the exception of a structural alteration that increases the lipophilicity of AZL and potentially improves its oral bioavailability [7]. Ojima and colleagues showed that azilsartan is more potent with more slowly dissociating AT_1 antagonist properties compared with other agents in the ARB class [8]. AZL has exhibited dose-dependent suppression of increases in plasma glucose levels following an oral glucose tolerance test, improved insulin sensitivity, decreased epididymal adipose-tissue weight, suppression of plasminogen activator inhibitor type-1 and a dose-dependent reduction in myocardial infarction [9–12]. AZL is

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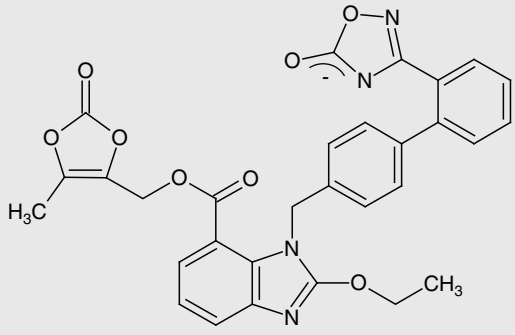
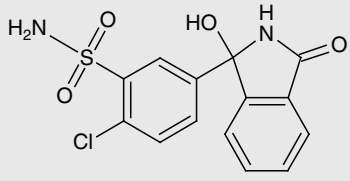
Drug summary.	
Drug name	Azilsartan medoxomil + chlorthalidone
Phase	Already marketed
Indication	Treatment of hypertension, to lower blood pressure
Pharmacology description	Azilsartan medoxomil is a prodrug that is hydrolyzed within the gastrointestinal tract to azilsartan. Azilsartan medoxomil has a peak plasma concentration within 1.5–3 h, a terminal half-life of approximately 11 h, with an estimated renal clearance of 2.3 ml/min. Chlorthalidone is fully absorbed with serum concentrations peaking at 1 h and a terminal half-life of approximately 45 h
Route of administration	Orally
Chemical structure	Azilsartan medoxomil  Chlorthalidone 
Pivotal trial(s)	[35–37]

metabolized, primarily by CYP2C9, to a major metabolite (M-II) via *O*-dealkylation and a minor metabolite (M-I) via decarboxylation [13]. AZL reaches a peak plasma concentration within 1.5–3 h, a terminal half-life of approximately 11 h, with an estimated renal clearance of 2.3 ml/min. No dose adjustments are required based on renal or hepatic function.

Pharmacological properties of CLD

Commonly referred to as a thiazide diuretic, CLD differs in structure from benzothiadiazines (e.g., hydrochlorothiazide [HCTZ]) and is more appropriately classified as a thiazide-like diuretic [14]. CLD is chemically related to sulfonamides, but exerts its antihypertensive effect at the distal convoluted tubule of the nephron similar to other thiazide diuretics. Following oral administration, CLD is fully absorbed with serum concentrations peaking at 1 h [15]. The terminal half-life of CLD is approximately 45 h [15]. CLD enters (half-life ~15 min) and concentrates rapidly in erythrocytes, but is slowly released from this compartment, which may explain its prolonged terminal half-life compared with HCTZ (~6–10 h) [14]. The natriuretic effects of CLD are said to be highest at 18 h and last more than 48 h [16]. A major portion of CLD is excreted, unchanged, in the urine. No significant drug interactions have been identified to date.

Clinical efficacy trials of AZL

Clinical trials comparing AZL with placebo or active controls, both as monotherapy and combination therapy, are summarized in Table 1 [17–22]. AZL was compared with olmesartan in two trials [17,18], valsartan in two trials [18,19], candesartan in one trial versus azilsartan (rather than AZL like the other trials) [20] and ramipril in one trial [21]. The trials ranged in duration from 6 to 24 weeks while enrollment ranged from 622 to 1291 participants. In general, AZL was found to be more effective at improving the trials' primary end point of clinic or ambulatory systolic BP (SBP) versus each of these comparators. A recently published meta-analysis of these trials showed that AZL use reduced clinic SBP/diastolic BP (DBP) by approximately 4/3 mmHg more than active controls [23]. Similar statistically significant findings for improving ambulatory BP monitoring (ABPM) were seen versus control ($p < 0.00001$). Additionally, the combination

Table 1. Clinical trials reporting the efficacy of azilsartan medoxomil in patients with hypertension.

Study (year)	Number	Inclusion criteria	Treatment, dose	Duration	Primary outcome	Results	Ref.
Azilsartan medoxomil monotherapy trials							
Bakris *et al.* (2011)	1275	Clinic SBP 150–180 mmHg or 24-h mean SBP 130–170 mmHg	AZL 20, 40, 80 mg q.d. or OLM 40 mg q.d. or Placebo	6 weeks	Change in 24-h mean SBP by ABPM from baseline	AZL 80 mg (-14.6) significantly improved mean SBP more than OLM (-12.6) ($p = 0.038$), while the 40 mg (-13.5) dose was non-inferior	[17]
White *et al.* (2011)	1291	Clinic SBP 150–180 mmHg and 24-h mean SBP 130–170 mmHg	AZL 40, 80 mg q.d. or OLM 40 mg q.d. or VAL 320 mg q.d. or Placebo	6 weeks	Change in 24-h mean SBP by ABPM from baseline	AZL 80 mg (-14.5 ± 0.7) significantly improved mean SBP more than OLM (-12.0 ± 0.7) and VAL (–10.2 ± 0.7) ($p < 0.01$ for both). AZL 40 mg (-13.4 ± 0.7) non-inferior to OLM	[18]
Sica *et al.* (2011)	984	Clinic SBP 150–180 mmHg and 24-h mean SBP 130–170 mmHg	AZL 40, 80 mg q.d. or VAL 320 mg q.d.	24 weeks	Change in 24-h mean SBP by ABPM from baseline	AZL 40 mg (-14.9) and 80 mg (-15.3) significantly improved 24-h mean SBP more than VAL (-11.3; $p < 0.001$ for both)	[19]
Rakugi *et al.* (2012)	622	Japanese patients with sitting DBP 95–<110 mmHg and sitting SBP 150–<180 mmHg	AZL 20–40 mg q.d. or CAND 8–12 mg q.d.	16 weeks	Change in trough seated clinic DBP from baseline	AZL (-12.4 ± 9.9 mmHg) significantly reduced DBP more than candesartan (-9.8 ± 8.5 mmHg; $p = 0.0003$)	[20]
Bonner *et al.* (2013)	884	Clinic SCP 150–180 mmHg	AZL 20–80 mg q.d. or RAM 2.5–10 mg q.d.	24 weeks	Change in trough seated 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)	[21]
Azilsartan medoxomil combination trial							
Weber *et al.* (2014)	566	Stage 2 HTN	AZL 40, 80 mg q.d. + AML 5 mg q.d. or AML 5 mg q.d. + placebo	6 weeks	Change in 24-h mean SBP by ABPM from baseline	AZL 40 mg and 80 mg + AML 5 mg significantly reduced 24-h mean SBP (-24.8 and -24.5) vs. AML + placebo (-13.6; $p < 0.001$ for both)	[23]

BP reductions are in mmHg.
ABPM: Ambulatory blood pressure monitoring; AML: Amlodipine; AZL: Azilsartan medoxomil; CAND: Candesartan; CLD: Chlorthalidone; DBP: Diastolic blood pressure; FDC: Fixed-dose combinations; HCTZ: Hydrochlorothiazide; HTN: Hypertension; OLM: Olmesartan; q.d.: Once daily; RAM: Ramipril; SBP: Systolic blood pressure; VAL: Valsartan.

of AZL plus amlodipine reduced SBP by a significantly greater amount than amlodipine alone [22].

Clinical efficacy trials of CLD

CLD has been the thiazide-like diuretic of choice in many large outcome trials in patients with hypertension [24–27]. Despite the availability of these data, HCTZ is the thiazide predominantly used in clinical practice. However, pharmacologic and therapeutic differences do exist between the agents [28] and there are very limited data showing that HCTZ improves CV outcomes. A randomized, single-blind, 8-week crossover trial evaluated the effect of CLD and HCTZ on changes in 24-h mean systolic and diastolic ambulatory BP in 30 patients with stage 1 or 2 hypertension [29]. CLD was initiated at 12.5 mg/day and

Table 2. Clinical trials reporting the efficacy of combination azilsartan medoxomil + chlorthalidone in patients with hypertension.

Study (year)	Design	Number	Inclusion criteria	Treatment, dose	Duration	Primary outcome	Secondary outcome(s)	Ref.
Bakris *et al.* (2012)	R, DB, DD Titrate-to-target	609	≥18 years old with stage 2 (primary) HTN Mean age: 56.4 years	AZL 40 mg daily + CHLOR or HCTZ 12.5–week 6, titrated to 25 mg daily until week 10 if needed	10 weeks	Change in trough, seated clinic SBP at weeks 6 and 10	Change from baseline in clinic DBP and 24-h mean SBP and DBP by ABPM	[36]
Cushman *et al.* (2012)	R, DB Forced-titration	1071	≥18 years old, SBP 160–190 mmHg Mean age: 57 years	AZL/CHLOR 40/25 mg daily AZL/CHLOR 80/25 mg daily OLM/HCTZ 40/25 mg daily	12 weeks	Change from baseline in trough (~24 h post-dose), seated, clinic SBP at week 12	Changes from baseline in clinic DBP, 24-h mean SBP and DBP measured by ABPM, and other ABPM parameters including trough mean BP (22–24 h post-dosing)	[37]
Sica *et al.* (2012)	R, DB Factorial study	1714	≥18 years old, SBP 160–190 mmHg Mean age: 57 years	AZL 0, 20, 40, 80 mg daily and/or CHLOR 0, 12.5, 25 mg daily	8 weeks	Change in trough (~22–24 h post-dose) SBP by ABPM at week 8	Change in trough SBP by ABPM in black patients and change in clinic SBP in all patients	[35]

ABPM: Ambulatory blood pressure monitoring; AZL: Azilsartan; BP: Blood pressure; CHLOR: Chlorthalidone; DB: Double-blind; DBP: Diastolic blood pressure; DD: Double dummy; HCTZ: Hydrochlorothiazide; HTN: Hypertension; OLM: Olmesartan; R: Randomized; SBP: Systolic blood pressure.

titrated to 25 mg/day while HCTZ was initiated at 25 mg/day and titrated to 50 mg/day. CLD was associated with a larger reduction in mean 24-h SBP from baseline (-12.4 ± 1.8 mmHg) versus HCTZ (-7.4 ± 1.7 mmHg; p = 0.054). This effect was primarily driven by more substantial differences in nighttime SBP reductions (-13.5 ± 1.9 vs. -6.4 ± 1.8 mmHg; p = 0.009).

Two meta-analyses have provided evidence of differences in BP lowering efficacy between these diuretics [30,31]. The first meta-analysis of 137 trials compared the BP lowering efficacy of CLD versus HCTZ [30]. Through the dosing range of 12.5–25 mg/day, CLD and HCTZ reduced SBP by -24 ± 6.7 and -14 ± 4.1 mmHg, respectively. A more recently published meta-analysis included data only from 26 placebo-controlled trials with CLD, HCTZ and bendroflumethiazide [31]. Using meta-regression techniques, the authors estimated that the approximate dose of bendroflumethiazide, CLD and HCTZ required to reduce the SBP by 10 mmHg was 1.4, 8.6 and 26.4 mg, respectively. These findings support the claim of CLD having greater potency than HCTZ.

A number of recently published observational studies and meta-analyses have re-evaluated the impact of CLD use on health outcomes in hypertensive patients. A retrospective cohort analysis of the Multiple Risk Factor Intervention Trial (MRFIT) showed that CLD (hazard ratio [HR]: 0.51; 95% CI: 0.43–0.61) and HCTZ (HR: 0.65; 95% CI: 0.55–0.75) use was associated with lower risk of cardiovascular events [32]. When compared with each other, CLD has a significantly lower risk of CV events versus HCTZ (HR: 0.79; 95% CI: 0.68–0.92). In contrast, an observational propensity score-matched cohort study of 29,873 older hypertensive patients showed no significant difference in adverse cardiovascular events or deaths with CLD versus HCTZ (adjusted HR: 0.93; 95% CI: 0.81–1.06) [33]. A network meta-analysis of nine randomized trials in which at least one arm was based on either CLD or HCTZ showed that CLD was associated with a significant reduction in cardiovascular event risk versus HCTZ (relative risk [RR]: 0.79; 95% CI: 0.72–0.88) [34]. This finding was primarily driven by reductions in hospitalized heart failure (RR: 0.77; 95% CI: 0.61–0.98) rather than all-cause mortality (RR: 0.94; 95% CI: 0.82–1.09) or stroke (RR: 0.96; 95% CI: 0.76–1.21).

Clinical efficacy trials of combination AZL + CLD

To date, three randomized, double-blind clinical trials evaluating the effectiveness of a fixed-dose combination of AZL/CLD on BP control in 3394 patients with stage 2 hypertension have been published. Trial characteristics are highlighted in Table 2 [35–37]. Fixed-dose combinations of AZL/CLD were compared with their individual monotherapies [35], combination AZL/HCTZ [36] and with fixed-dose combinations of olmesartan/HCTZ [37]. Primary outcomes included changes from baseline in trough, seated SBP (via clinic) or 24 h BP over an 8- to 12-week period [35–37].

In a double-blind factorial study, the efficacy of fixed-dose combinations of AZL/CLD was compared with the respective individual monotherapies in 1714 hypertensive patients (≥18 years of age) with a clinic SBP of 160–190 mmHg [35]. During 8 weeks of double-blind treatment, patients were randomized to 1 of 11 active treatments: AZL 20, 40 or 80 mg and/or CLD 12.5 or 25 mg. Treatment assignment was stratified by race (i.e., black or non-black). The primary outcome was change in trough (22–24 h post-dose) SBP by ABPM at week 8. Baseline mean trough BP was 149–154/89–92 mmHg (via ABPM) and 163–166/94–96 mmHg (via clinic BP). At the conclusion of the study, the highest doses of fixed-dose combination AZL/CLD (40/25 and 80/25 mg) led to the greatest reduction in trough SBP by ABPM (-28.9 mmHg, similar for both doses) and clinic measurement (-39.8 mmHg) compared with the highest doses of AZL (80 mg, -15.1 mmHg via ABPM) and CLD (25 mg, -15.9 mmHg via ABPM; $p < 0.05$). All fixed-dose combinations of AZL/CLD led to significantly greater reductions in SBP compared with the respective individual monotherapies. The observed SBP reduction in black patients was similar to those observed in the total study population for the combination therapy.

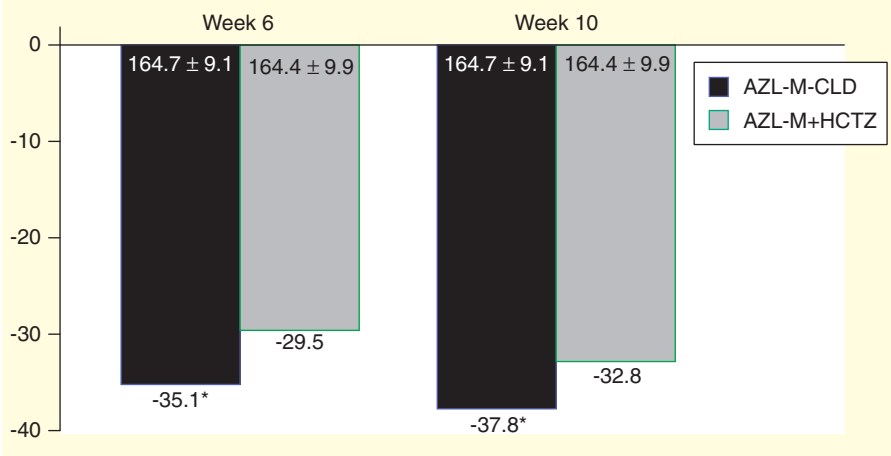


Figure 1. Effect of azilsartan medoxomil versus azilsartan/hydrochlorothiazide on change in trough sitting clinic systolic blood pressure (mmHg).
*$p < 0.001$.
AZL: Azilsartan medoxomil; CLD: Chlorthalidone; HCTZ: Hydrochlorothiazide.
Reproduced with permission from [36].

The efficacy of combination AZL/CLD was also compared with AZL combined with HCTZ in 609 adult patients with stage 2 hypertension [36]. In this 10-week titrate-to-target study, patients received 2 weeks of single-blind treatment with AZL 40 mg daily. Patients were then randomized to receive a forced addition of 12.5 mg of either CLD or HCTZ combined with AZL for 4 weeks. If target BP goals (mean trough, sitting clinic BP of <140/90 or <130/80 mmHg for patients with chronic kidney disease or diabetes) were not achieved by week 6, the diuretic dose was titrated up to 25 mg. Treatment was continued through week 10. The primary outcome was change in trough, seated clinic SBP at weeks 6 and 10. At week 6, patients randomized to AZL/CLD achieved greater reductions in clinic SBP compared with AZL/HCTZ (-35.1 vs -29.5 mmHg, respectively; $p < 0.001$) (Figure 1). At week 10, greater SBP reductions were attained with AZL/CLD compared with AZL/HCTZ (-37.8 vs -32.8 mmHg, respectively; $p < 0.001$). Similarly, significant reductions in mean 24-h SBP by ABPM were seen with AZL/CLD versus AZL/HCTZ at both 6 and 10 weeks ($p < 0.001$ for both) (Figure 2). Of note, only 30.8% of patients in the AZL/CLD group required the forced diuretic titration at week 6 compared with the 45.9% of patients treated with AZL/HCTZ ($p < 0.001$). However, it is important to note that the potencies of diuretics evaluated in this study may not be comparable. CLD has been described as 1.5- to 2.0-times more potent than HCTZ. Therefore, a dose of 25 mg of CLD would be estimated to be equivalent to 37.5–50 mg of HCTZ [29].

In a forced titration study, the efficacy of once-daily fixed-dose combinations of AZL/CLD (force titrated to 40/25 or 80/25 mg) was compared with a fixed-dose combination of olmesartan/HCTZ (force titrated to 40/25 mg) [37]. One thousand and seventy-one adult patients with a SBP between 160 and 190 mmHg were randomized for 12 weeks of treatment. The primary outcome was change from baseline in trough (24 h post-dose), seated, clinic SBP. At the conclusion of the study, both fixed-dose combinations of AZL/CLD led to greater reductions in clinic SBP compared with olmesartan/HCTZ (-42.5 mmHg, -44 vs -37.1 mmHg, respectively; $p < 0.001$). The authors concluded that AZL/CLD is more effective in reducing BP than olmesartan/HCTZ. Similar to the results of the aforementioned study, the doses of diuretics used may not be equipotent, although they are used in clinical practice.

Safety & tolerability of combination AZL + CLD

Despite the overall tolerability of AZL/CLD in clinical trials, a number of safety concerns have been acknowledged [35–37]. Withdrawals due to adverse events ranged from 4.1 to 14.5% across various AZL/CLD doses [35–37] compared with 7.1% with olmesartan/HCTZ [37], 7.3% with AZL/HCTZ [36], 2.5–3.8% with CLD monotherapy and 1.9–3.9% with AZL monotherapy [35]. Reported adverse events appear to be dose-related and are more frequently associated with combination therapy. Commonly reported side effects include dizziness, hypotension and transient, and non-progressive elevations in serum creatinine (Table 3).

In premarketing clinical trials, safety of AZL and its combination therapies was evaluated in 3900 patients with hypertension over 6–12 months of treatment [15]. Similar to the findings

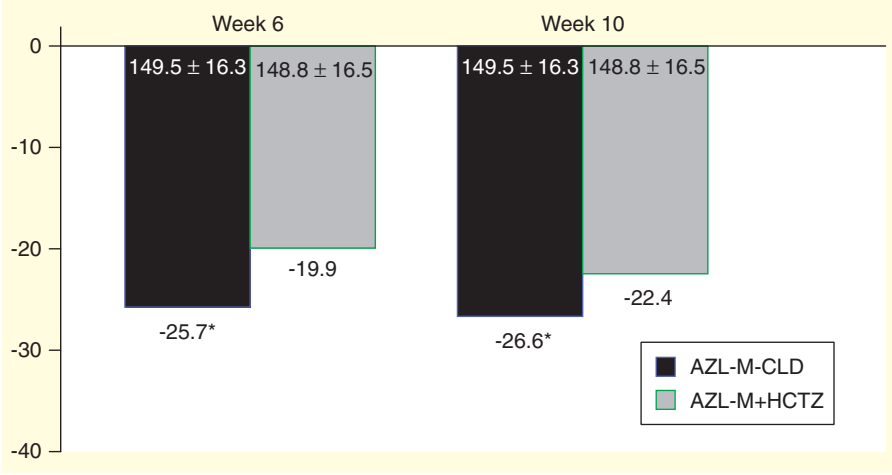


Figure 2. Effect of azilsartan medoxomil versus azilsartan/hydrochlorothiazide on change in mean 24 h systolic blood pressure (mmHg) by ambulatory blood pressure monitoring.
*$p < 0.001$.
AZL: Azilsartan medoxomil; CLD: Chlorthalidone; HCTZ: Hydrochlorothiazide.
Reproduced with permission from [36].

observed in clinical trials, the adverse events related to AZL/CLD therapy were generally mild and transient in nature.

Expert commentary

What, if any, improvement does the drug hold over other therapies?

Both AZL and the combination of AZL plus CLD have superior efficacy to other ARBs alone or in combination with HCTZ based on extensive evaluation in clinical trials. Of note, the superior efficacy is not offset by a large imbalance in clinically important adverse events.

What, if any, impact is this drug likely to have on current treatment strategies?

While AZL alone or in combination with other therapies is not likely to affect current treatment strategies for moderate and severe hypertension, its efficacy, particularly as a combination therapy, could improve BP control rates in practice and therefore translate to reductions in complications of hypertension including stroke and congestive heart failure.

How likely are providers to prescribe the drug?

In the USA, physicians have been willing to prescribe the drug but its uptake has been slow based on coverage by pharmacy benefit plans and insurance companies. In countries in which restrictions are less strict, it is likely that physicians will prescribe both AZL as well as the combination with CLD in patients requiring renin–angiotensin system blockade with moderate responses to other agents in the class.

What data are still needed?

Efficacy and general safety data are extensive with AZL alone and in combination with diuretics and amlodipine. It is not likely that further research with this agent on cardiovascular

Table 3. Commonly reported drug discontinuations and adverse events with combination azilsartan medoxomil + chlorthalidone.

Study (year)	Reason for drug discontinuation	ADEs reported with AZL + CHLOR	Clinical considerations	Ref.
Bakris *et al.* (2012)	Dizziness 1.0% Increased SCr 4.0%	Dizziness 12.3% Increased SCr 12.9% Headache 5.3% Fatigue 3.6% Asthenia 3.0% Hypotension 2.3% Upper respiratory tract infection 1.3%	Total drug discontinuation rates and ADEs were slightly higher in AZL + CHLOR group, although not significantly	[36]
Cushman *et al.* (2012)	Dizziness 1.1–3.7% Increased SCr 0.8–3.4% Hypotension 0.3–3.4%	Increased SCr 18.6–22.2% Dizziness 11.5–16.5% Fatigue 4–9.3% Headache 3.7–5.4% Increased uric acid 4.8–5.4%	The frequency and total ADES was higher in the AZL + CHLOR group compared with OLM + HCTZ	[37]
Sica *et al.* (2012)	No mention of specific ADEs	Increased SCr 2.6–19.9% Dizziness 1.3–13.7% Headache 0.7–12.2% Increase uric acid 2.7–35.9%	ADEs were dose related and more common in AZL + CHLOR group, however, hypotension episodes were infrequent with combined therapy (0.6–3.1%)	[35]

ADEs: Adverse drug events; AZL: Azilsartan medoxomil; CHLOR: Chlorthalidone; HCTZ: Hydrochlorothiazide; OLM: Olmesartan; SCr: Serum creatinine.

outcomes will be performed as it is not a regulatory requirement nor financially feasible in this era of clinical medicine.

Five-year view

The efficacy of AZL is impressive and it is likely that its clinical utility will gradually increase over the next 5 years in clinical practice. As there are few to no new pharmacotherapies likely for development in the hypertension space, AZL and AZL in combination with CLD will be recognized as a superior agent for the management of hypertension, particularly for those individuals with stage 2 (moderate-to-severe) hypertension.

Financial & competing interests disclosure

WB White is presently 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. The authors have no other 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 apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Initiation of drug therapy for treating hypertension often requires combination therapy in order to reach treatment goals.
- Azilsartan medoxomil (AZL) has been added to the thiazide-like diuretic chlorthalidone (CLD) in a fixed-dose combination.
- Clinical trials have shown the combination of AZL/CLD to reduce blood pressure to a greater amount compared with both their individual monotherapies and the combination of other angiotensin receptor blockers with hydrochlorothiazide.
- The adverse events related to AZL/CLD therapy are generally mild and transient in nature and similar to the individual components.
- This fixed-dose combination could help improve blood pressure control rates in practice and potentially translate into reductions in complications of hypertension.

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•• **This meta-analysis of 42 trials and nearly 11,000 participants showed that adding a drug from a 2nd class provides approximately five-times greater blood pressure lowering than doubling the dose of the first drug.**

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