Brand Name: Edarbyclor

Generic Name: azilsartan medoxomil and chlorthalidone

Manufacturer[1]**:** Takeda Pharms USA

Drug Class[2,3,4,5]**:** Antihypertensive, Angiotensin II Receptor Blocker; Diuretic, Thiazide

Uses: **Labeled Uses**[1,2,3,4,5] Hypertension, treatment of edema associated with heart failure or nephrotic syndrome.
Unlabeled Uses[1,2,3,4,5] None

Mechanism of Action:[2,3]

Azilsartan medoxomil is a prodrug which is hydrolyzed to azilsartan in the gastrointestinal tract. The active moiety, azilsartan, is an angiotensin II antagonist that selectively blocks the binding of angiotensin II to the AT1 receptors. By blocking the binding of angiotensin II to the AT1 receptors, azilsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II and therefore promotes vasodilation and decreased aldosterone effects. Azilsartan displays greater than 10,000-fold affinity for AT1 receptor, compared with binding to AT2 receptor, and has not shown affinity to any other receptors or ion channels of cardiac significance. The breakdown of bradykinin appears unaffected by azilsartan.

Chlorthalidone is a diuretic that increases excretion of sodium and chloride at the ascending limb of the loop of Henle in the nephron, resulting in decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate and renal plasma flow.

Pharmacokinetics[2,3,4,5]**: Absorption:**

T_{max}	Azilsartan- 3 hours Chlorthalidone- 1 hour
V_d	Azilsartan-16 L Chlorthalidone not reported
$t_{½}$	Azilsartan- 12 hours Chlorthalidone- 45 hours
Clearance	Azilsartan-Renal: 2.3mL/min (42%, 15% unchanged) Azilsartan-Fecal: 55% Chlorthalidone- Renal: unchanged
Protein binding	Azilsartan- Albumin:greater than 99% Chlorthalidone- 75%; Albumin:58%
Bioavailability	Azilsartan- Oral: 60% (Food has no effect) Chlorthalidone- Oral: 65%

Metabolism: Azilsartan is a prodrug metabolized by the liver via CYP2C9. Chlorthalidone is metabolized hepatically.

Elimination:. Azilsartan is primarily eliminated by the fecal route (55%, with approximately 42% being eliminated in the urine with 15% being unchanged. The majority of chlorthalidone is eliminated unchanged by the kidneys into the urine.

Efficacy:

> **Sica, Domenic, George Bakris, William White, Michael Weber, William Cushman, Patrick Huang, Andrew Roberts, and Stuart Kupfer. Blood Pressure–Lowering Efficacy of the Fixed-Dose Combination of Azilsartan Medoxomil and Chlorthalidone: A Factorial Study. 14(5); 2012** [6]

Study Design: This was a phase 3, randomized, double-blind, factorial study comparing the antihypertensive efficacy and safety of a fixed dose combinations containing azilsartan medoxomil and chlorthalidone with each monotherapy and conducted in 175 sites in multiple countries.

Description of Study: *Methods:* Before randomization, there was a 3-4 week washout period of patients previously on BP-lowering agents. After the washout/run-in was complete, eligible patients were randomized to 8 weeks of double-blind treatment with AZL-M 20 mg, 40 mg, or 80 mg; CLD 12.5 or 25 mg; or 1 of the 6 combinations of these doses (AZL-M/CLD: 20/12.5 mg, 40/12.5 mg, 80/12.5 mg, 20/25 mg, 40/25 mg, and 80/25 mg). At randomization, each patient was required to have a clinic SBP ≥160 mm Hg and ≤190 mm Hg. Exclusion criteria included known or suspected secondary hypertension or severe diastolic hypertension; advanced renal disease; clinically relevant or unstable cardiovascular diseases present within 6 months of enrollment; poorly controlled diabetes; clinically significant hepatic abnormalities; or abnormal potassium (K+). *Results:*1470 (85.7%) patients completed the study as planned. Across treatment groups, the range of mean baseline trough BP by ABPM was 149 to 154 mm Hg/89 to 92 mm Hg, and the range of mean trough clinic BP was 163 to 166 mm Hg/94 to 96 mm Hg. At week 8, the highest doses of AZL-M/CLD (40/25 mg and 80/25 mg) produced clinically and statistically significantly greater reductions in trough SBP by both ABPM (primary end point) and clinic measurement (key secondary end point) compared with the highest doses of AZL-M and CLD monotherapy. Similarly, each of the 6 individual AZL-M/CLD doses led to significantly greater reductions in both clinic and ABPM measures of trough SBP compared with their respective AZL-M and CLD components. For the ABPM results, greater reductions were also seen with AZL-M/CLD at each hour of the ambulatory recording . Reductions in trough SBP by ABPM observed with each dose of AZL-M/CLD were nearly additive relative to their monotherapy components. For both the ABPM and clinic measures, reductions in trough SBP were generally dose-related, although the 80/25-mg dose of AZL-M/CLD did not afford consistent incremental reduction compared with the 40/25-mg dose. As with the systolic results, there were significantly greater reductions in trough DBP with each dose of AZL-M/CLD compared with the respective monotherapy components . Consistently greater diastolic reductions were maintained with AZL-M/CLD throughout the 24-hour recording interval. Each of the 6 AZL-M/CLD doses led to a significantly higher proportion of patients who achieved BP targets compared with their respective AZL-M and CLD components. The proportion of patients who achieved both a target SBP <140 mm Hg and a target DBP <90 mm Hg ranged between 70% and 85% in the FDC groups, between 30% and 52% with AZL-M monotherapy, and between 34% and 51% with CLD monotherapy .

Limitations: This study was sponsored by Takeda Global Research and Development Center. Takeda Pharmaceuticals is the company responsible for the production and marketing of Edarbyclor.

Conclusion: These are the first studies using CLD together with an ARB in an FDC. The reduction in BP with this FDC is significantly greater than what has been observed with a similar dose of HCTZ given in an FDC with any of a number of ARBs. The availability of an FDC with an ARB and CLD, capable of reducing BP to this degree, offers the opportunity to reframe the paradigm for the treatment of hypertension when multidrug therapy is necessary.

Zaiken, Kathy, and Judy Cheng. **Azilsartan Medoxomil: A New Angiotensin Receptor Blocker. 33(11); 2011;1577-1589** [7]

Study Design: Double blind, randomized, placebo-controlled study to evaluate the efficacy and safety of azilsartan when coadministered with chlorthalidone.

Description of Study: *Methods*: A total of 551 subjects aged ≥ 18 years (average age not reported) with SBP between 160 and 190 mm Hg were randomized to receive placebo + chlorthalidone 25 mg daily; azilsartan 40 mg + chlorthalidone 25 mg daily; or azilsartan 80 mg + chlorthalidone 25 mg daily for 6 weeks. .*Outcome Results:* At the end of the treatment period, chlorthalidone alone decreased SBP by 16 mm Hg. There was no difference between the azilsartan + chlorthalidone groups (40 mg: –31.72 mm Hg; 80 mg: –31.3 mm Hg [$P >$ 0.05), but both groups compared with chlorthalidone alone significantly reduced SBP (both, $P < 0.05$). AEs reported in the azilsartan groups included hypotension (n= 5), dizziness (n = 4), and asthenia (n= 1). The study authors reported that azilsartan produced further reduction of BP when used with chlorthalidone.

Limitations: This study, along with others, have only identified the clinical effectiveness of azilsartan in treating hypertension. There are limited data on the use of azilsartan evaluating the effect in long-term vascular outcomes. Most of the information in this study is from information submitted by the manufacturer to the FDA to gain approval.

Conclusion: Azilsartan, alone, or in combination with chlorthalidone seems to be very efficacious in treating hypertension. This study demonstrated its higher efficacy when coadministered with chlorthalidone. Azilsartan also has a favorable safety profile when used with diuretics such as chlorthalidone. However, as with most diuretics, this study does mention the use of proper monitoring of creatinine and renal function when administering chlorthalidone with azilsartan for the treatment of hypertension. Further research investigating these potential roles will help establish a place for azilsartan in cardiovascular disease management, in addition to hypertension management. Currently, azilsartan should only be considered as an alternative ARB for hypertension management. The amount of clinical trials to regarding azilsartan is extremely limited to date.

Cushman, William, George Bakris, William White, Michael Weber, Domenic Sica, Andrew Roberts, Eric Lloyd, and Stuart Kupfer. **Azilsartan Medoxomil Plus Chlorthalidone Reduces Blood Pressure More Effectively Than Olmesartan Plus Hydrochlorothiazide in Stage 2 Systolic Hypertension. 60(2); 2012** [8]

Study Design: Randomized, double-blind, forced-titration study comparing the antihypertensive efficacy and safety of an FDC containing azilsartan medoxomil and chlorthalidone with and FDC containing olmesartan medoxomil and hydrochlorothiazide in patients with stage 2 primary systolic hypertension.

Description of Study: *Methods*: Men and women who were ≥ 18 years of age and had primary hypertension were recruited from 130 investigative sites in the United States and Canada. 1071 met the entry criteria and were randomized to 1 to 3 active treatment groups; 892 randomized patients completed the study as planned. The three treatment groups were as follows: azilsartan medoxomil/chlorthalidone 40/25 mg; olmesartan/ hydrochlorothiazide 40/25 mg; azilsartan medoxomil/chlorthalidone 80/25 mg. The washout period was completed and eligible patients were randomized to 12 weeks of double-blind treatment with one of the following dosing strategies: (1) azilsartan medoxomil/ chlorthalidone 20/12.5 mg to 40/12.5 mg to 40/25.0 mg; (2) azilsartan medoxomil/chlorthalidone 40/12.5 mg to 80/12.5 mg to 80/25.0 mg; or (3) olmesartan/ hydrochlorothiazide 20/12.5 mg to 40/12.5 mg to 40/25.0 mg. In each group, drug was force titrated regardless of BP at weeks 4 and 8. *Outcome Results*: The percentage of patients who achieved an SBP of <140 mm Hg was statistically significantly greater with azilsartan medoxomil/chlorthalidone 80/25 mg (87.3%) compared with olmesartan/ hydrochlorothiazide 40/25 mg (80.2%; P=0.007) but not significantly different for azilsartan medoxomil/ chlorthalidone 40/25 mg (84.9%) versus olmesartan/hydrochlorothiazide (P=0.08). Both azilsartan

medoxomil/chlorthalidone groups had statistically significantly more subjects reach an SBP of <130 or <120 mm Hg compared with the olmesartan/ hydrochlorothiazide group. Similarly, the percentage of patients who achieved a target BP of <140/90 mm Hg
(81.4%, 83.9%, and 74.6%) or <130/80 mm Hg (56.1%, 60.6%, and 41.0%) was significantly greater in both azilsartan medoxomil/chlorthalidone groups than the olmesartan/ hydrochlorothiazide group.

Limitations: This study was sponsored by Takeda Global Research and Development Center. Takeda Pharmaceuticals is the company responsible for the production and marketing of Edarbyclor. Although this forced-titration design gives the most accurate reflection of true differences in the regimens being compared, it is different from the usual clinical practice of titrating medications to achieve a specified BP goal. A consequence of this design is that the BPs achieved are often lower than would be necessary to reach BP goals. The lower levels of achieved BP may have exaggerated the elevations in creatinine observed, especially in the 80/25-mg azilsartan medoxomil/chlorthalidone group. Despite greater uric acid elevations in the azilsartan medoxomil/ chlorthalidone groups compared with the olmesartan/hydrochlorothiazide group, reports of gout were infrequent and similar across groups; however, the relatively short study duration does not inform potential long-term differences.

Conclusion: The azilsartan/chlorthalidone 40/25 mg once daily provides a well-tolerated and more effective treatment for stage 2 systolic hypertension than olmesartan/hydrochlorothiazide 40/25 mg. The implication of these results is that this single-pill combination of 2 antihypertensive drugs may provide BP control to recommended target BP levels for a higher proportion or of hypertensive patients than other 2-drug FDCs. There was a moderately higher adverse discontinuation rate for the higher 80/25 mg dose of azilsartan medoxomil/chlorthalidone.

Contraindications[2,3,4,5]**:**

Hypersensitivity to chlorthalidone or any component of the formulation; cross-sensitivity with other thiazides or sulfonamides; anuria; renal decompensation; pregnancy.

Precautions[2,3,4,5]**:**

Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur.

Photosensitivity: Photosensitization may occur.

Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with thiazide or sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated.

Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

Hypercalcemia: Thiazide diuretics may decrease renal calcium excretion; consider avoiding use in patients with hypercalcemia.

Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations.

Hypokalemia: Use with caution in patients with hypokalemia; correct before initiating therapy.

Renal impairment: Avoid in severe renal disease (ineffective).

In patients with renal disease, chlorthalidone may precipitate azotemia. If progressive renal impairment becomes evident, as indicated by increased blood urea nitrogen, consider withholding or discontinuing diuretic therapy.

Systemic lupus erythematosus (SLE): Can cause SLE exacerbation or activation.

Pregnancy: second and third trimesters; reduces fetal renal function and may cause fetal and neonatal morbidity and death; discontinue therapy as soon as possible when pregnancy is detected.

Congestive heart failure: severe; increased risk of oliguria, progressive azotemia, and rarely, acute renal failure and/or death.

Pediatric Use: Safety and effectiveness in pediatric patients under 18 has not been established.

Adverse Effects [2,3,4,8]**:**

Occurring <10% of patients

Cardiovascular

Hypotension 1.7%
Syncope 0.3%

Dermatologic

Rash

Endocrine/Metabolic

Hypokalemia 1.7%
Increased uric acid level
Serum cholesterol raised

Gastrointestinal

Nausea 0.3%

Musculoskeletal

Spasm 0.3%

Neurologic

Asthenia 0.3%
Dizziness 8.9%
Headache

Postural dizziness 0.3%

Renal

Renal failure
Serum blood urea nitrogen raised
Serum creatinine reaised 2%

.Respiratory

Cough 0.3%

Other

Fatigue 2%

Drug Interactions[2,3,4,5]:

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

May enhance the orthostatic hypotensive effect of Thiazide Diuretics. *Risk C: Monitor therapy*

- *Alcohol (ethyl)*
- *Antihypertensives*
- *Herbs (hypotensive properties)*
- *Pentoxifylline*
- *Prostacyclin analogues*

Alfuzosin: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

May enhance the orthostatic hypotensive effect of Thiazide Diuretics. *Risk C: Monitor therapy*

- Analgesics (opioids)
- Barbiturates
- MAO inhibitors

Antidiabetic Agents: Thiazide Diuretics may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Beta2-Agonists: May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Carbamazepine: Thiazide Diuretics may enhance the adverse/toxic effect of Carbamazepine. Specifically, there may be an increased risk for hyponatremia. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled or systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk X: Avoid combination*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Oxcarbazepine: Thiazide Diuretics may enhance the adverse/toxic effect of Oxcarbazepine. Specifically, there may be an increased risk for hyponatremia. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Rituximab: Antihypertensives may enhance the hypotensive effect of Rituximab. *Risk D: Consider therapy modification*

Sodium Phosphates: Diuretics may enhance the nephrotoxic effect of Sodium Phosphates. Specifically, the risk of acute phosphate nephropathy may be enhanced. Management: Consider avoiding this combination by temporarily suspending treatment with diuretics, or seeking alternatives to oral sodium phosphate bowel preparation. If the combination cannot be avoided, hydrate adequately and monitor fluid and renal status. *Risk D: Consider therapy modification*

Topiramate: Thiazide Diuretics may enhance the hypokalemic effect of Topiramate. Thiazide Diuretics may increase the serum concentration of Topiramate. Management: Monitor for increased topiramate levels/adverse effects (e.g., hypokalemia) with initiation/dose increase of a thiazide diuretic. Closely monitor serum potassium concentrations with concomitant therapy. Topiramate dose reductions may be necessary. *Risk D: Consider therapy modification*

Vitamin D Analogs: Thiazide Diuretics may enhance the hypercalcemic effect of Vitamin D Analogs. *Risk C: Monitor therapy*

Herb/Nutraceutical: Avoid herbs with *hypertensive* properties (bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng [American], kola, licorice); may diminish the antihypertensive effect of chlorthalidone. Avoid herbs with *hypotensive* properties (black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse); may enhance the hypotensive effect of chlorthalidone.

Dosing/Administration[2,3,4,5]:

Adult Dosing

Hypertension: Oral: 25-100 mg/day or 100 mg 3 times/week; usual dosage range (JNC 7): 12.5-25 mg/day

Edema: Initial: 50-100 mg/day or 100 mg on alternate days; maximum dose: 200 mg/day

Heart failure-associated edema: 12.5-25 mg once daily; maximum daily dose: 100 mg (ACC/AHA 2009 Heart Failure Guidelines)

Pediatrics (≥4 years of age)

Safety and efficacy not established in pediatric patients

Elderly

Oral: Initial: 12.5-25 mg/day or every other day; there is little advantage to using doses >25 mg/day

Renal impairment

Mild or moderate renal impairment: no dosage adjustment necessary.

Progressive renal impairment: withhold or discontinue treatment.

Cl_{cr} <10 mL/minute: Avoid use. Ineffective with low GFR.

Hepatic impairment

Mild or moderate hepatic dysfunction: no azilsartan medoxomil dosage adjustment necessary; chlorthalidone may precipitate hepatic coma

Use in special circumstances:

Pregnancy [3,4,5]**:** Adverse events were not observed in animal reproduction studies. Chlorthalidone crosses the placenta and can be detected in cord blood and amniotic fluid. Maternal use may cause may cause fetal or neonatal jaundice, thrombocytopenia, or other adverse events observed in adults. Use of thiazide diuretics during normal pregnancies is not appropriate; use may be considered when edema is due to pathologic causes (as in the nonpregnant patient); monitor. Drugs that affect the renin-angiotensin system (ACEi, ARB) used in the 2nd or 3rd trimester decrease fetal renal function and increase neonatal morbidity and mortality.

Lactation [3]**:** Enters breast milk/not recommended.

Overdosage[5]**:**

Azilsartan medoxomil

Limited data are available related to overdosage in humans. During controlled clinical trials in healthy subjects, once daily doses up to 320 mg of azilsartan medoxomil were administered for 7 days and were well tolerated. In the event of an overdose, supportive therapy should be instituted as dictated by the patient's clinical status. Azilsartan is not dialyzable.

Chlorthalidone

Symptoms of acute overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. The oral LD50 of the drug in the mouse and the rat is more than 25,000 mg/kg body weight. The minimum lethal dose (MLD) in humans has not been established. There is no specific antidote, but gastric lavage is

recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose-saline with potassium, administered with caution.

Conclusion:

Azilsartan plus chlorthalidone is an effective therapy for people with hypertension. Chlorthalidone has been approved for years as a diuretic and has shown efficacy for treating hypertension. Clinical studies to date have reported that azilsartan plus chlorthalidone is as efficacious as other ARBs, ACE inhibitors, and calcium channel blockers in reducing blood pressure. This new medication has also noted minimal side effects when compared to the other antihypertensives. Further research investigating its use in long term vascular outcomes, such as improving mortality and morbidity in patients with heart failure, history of myocardial infarction, and neuropathy still need to be performed to discover the potential benefits of this new angiotensin receptor blocker plus thiazide diuretic. As far as this combination drug's place in therapy, I would recommend a physician to first try an older alternative of an ACE-inhibitor or an ARB with proven efficacy before placing the cost burden on a patient. If initial therapy fails at optimizing blood pressure, then it would be appropriate to begin therapy with azilsartan plus chlorthalidone.

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