Drug Monograph

Drug/Drug Class:	**Edarbyclor® (azilsartan medoxomil and chlorthalidone) Tablet/ Angiotensin II Receptor Blocker and Diuretic Combination**
Prepared for:	MO HealthNet
Prepared by:	ACS, A Xerox Company

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each tablet of Edarbyclor® 40/12.5 mg tablets contains 40 mg of azilsartan and 12.5 mg of chlorthalidone. Each tablet of Edarbyclor® 40/25 mg contains 40 mg azilsartan and 25 mg chlorthalidone. Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015
Summary of Findings:	Edarbyclor® is a fixed-dose combination of an ARB (azilsartan) and a thiazide-like diuretic (chlorthalidone) that has demonstrated efficacy for the treatment of moderate or severe hypertension. Edarbyclor® has shown to be more effective than each azilsartan and chlorthalidone as monotherapy in patients with hypertension that requires a multiple drug regimen.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Hypertension, or high blood pressure, is a chronic medical condition in which blood pressure is elevated at levels of 140 mmHg or greater systolic and/or 90 mmHg or greater diastolic. High blood pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Hypertension typically has no symptoms and adults of all ages and backgrounds can develop hypertension. The risk of developing the condition increases with age, with more than half of people over age 60 becoming affected. Hypertension impacts approximately 75 million Americans, or nearly one in three adults and it is estimated that nearly one billion people are affected worldwide.

Dosage Form(s) [1]

Each tablet of Edarbyclor® 40/12.5 mg tablets contains 40 mg of azilsartan and 12.5 mg of chlorthalidone. Each tablet of Edarbyclor® 40/25 mg contains 40 mg azilsartan and 25 mg chlorthalidone.

Manufacturer

Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015

Indication(s) [1]

Edarbyclor® contains an angiotensin II receptor blocker (ARB) and a thiazide-like diuretic and is indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled on monotherapy and may be used as initial therapy if a patient is likely to need multiple drugs to achieve blood pressure goals.

Clinical Efficacy[1-8] (mechanism of action/pharmacology, comparative efficacy)

Azilsartan medoxomil is the prodrug form of azilsartan. It is hydrolyzed to azilsartan, the active metabolite, in the GI tract during absorption. It blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues including vascular smooth muscle and the adrenal gland.

Chlorthalidone is a monosulfamyl diuretic and antihypertensive agent that increases excretion of sodium and chloride. It directly affects the distal convoluted tubule of the nephron, resulting in decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate and renal plasma flow. It is believed that this sodium and water depletion provide its antihypertensive effect.

PHARMACOKINETICS (1,2,5-8)

	Azilsartan	**Chlorthalidone**
Protein binding	> 99%	75%
Volume of distribution	16 L	3 to 13 L/kg
Metabolism	O-dealkylation and decarboxylation via CYP2C9.	Unidentified metabolites.
Excretion	Feces (55%) Urine (42%)	Urine (50% to 74%) Feces
Half-life	11 hours	40 to 89 hours

The approval of azilsartan and chlorthalidone was primarily based on 5 randomized controlled clinical trials involving a total of 5310 patients with moderate or severe hypertension. Results from these studies showed that azilsartan and chlorthalidone demonstrated statistically significant reductions in blood pressure compared to each as monotherapy and was superior to the fixed-dose combination of olmesartan and hydrochlorothiazide at maximum respective doses. These studies also showed that azilsartan and chlorthalidone was effective in reducing blood pressure regardless of age, gender, or race.

Edarbyclor® vs. monotherapy of azilsartan or chlorthalidone

STUDY DESIGN	Multicenter, randomized, double-blind, active-controlled, parallel group, 8-week factorial clinical trial (n=1714).
INCLUSION CRITERIA	Patients with moderate to severe hypertension.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	The trial randomized patients with a baseline systolic blood pressure (BP) between 160 and 190 mmHg (mean, 165 mmHg) and a baseline diastolic blood pressure of < 119 mmHg (mean, 95 mmHg) to one of the 11 active treatment arms (once-daily azilsartan and chlorthalidone: 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg, 40 mg/25 mg, 80 mg/12.5 mg, 80 mg/25 mg; chlorthalidone 12.5 mg or 25 mg; azilsartan 20 mg, 40 mg, or 80 mg).
RESULTS	The 6 treatment combinations of azilsartan 20 mg, 40 mg, or 80 mg and chlorthalidone 12.5 mg or 25 mg resulted in statistically significant reductions in systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring (ABPM) and clinic measurements. The mean change from baseline in clinic systolic/diastolic BP at week 8 was -34/-14 mmHg, -37/-16 mmHg, and -37/-17 mmHg for azilsartan 20 mg, 40 mg, and 80 mg, respectively, and chlorthalidone 12.5 mg. The mean change from baseline in clinic systolic/diastolic BP at week 8 was -37/-16 mmHg, -40/-17 mmHg, and -

	40/-19 mmHg for azilsartan 20 mg, 40 mg, and 80 mg, respectively, and chlorthalidone 25 mg. The mean change from baseline in clinic systolic/diastolic BP at week 8 for azilsartan monotherapy was -20/-7 mmHg (20 mg), -23/-9 mmHg (40 mg), and -24/-10 mmHg (80 mg). The mean change from baseline in clinic systolic/diastolic BP at week 8 for chlorthalidone monotherapy was -21/-7 mmHg (12.5 mg) and -27/-9 mmHg (25 mg).
SAFETY	The most common adverse reactions in patients treated with combination therapy were dizziness and fatigue.

Edarbyclor® vs. olmesartan/hydrochlorthiazide

STUDY DESIGN	Double-blind, forced-titration, 12-week clinical trial (n=719).
INCLUSION CRITERIA	Patients with moderate to severe hypertension.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients received once-daily doses of azilsartan and chlorthalidone or olmesartan and hydrochlorothiazide in a double-blind, forced-titration regimen.
RESULTS	Azilsartan and chlorthalidone (40 mg/25 mg) was statistically superior ($p < 0.001$) to olmesartan and hydrochlorothiazide (40 mg/25 mg) in reducing systolic blood pressure. The mean change in systolic/diastolic BP at week 12 was -43/-19 mmHg for clinic patients receiving azilsartan and chlorthalidone (40 mg/25 mg) compared with -37/-16 mmHg for patients receiving olmesartan and hydrochlorothiazide (40 mg/25 mg). The mean change in systolic/diastolic BP at week 12 measured by ABPM at trough was -33/-20 mmHg and -26/-16 mmHg, respectively, in the same treatment groups.
SAFETY	Not specified.

Contraindications[1]

- Anuria

Warnings and Precautions[1]

- Excessive hypotension may occur; increased risk in volume and/or salt-depletion.
- Renal artery stenosis; increased risk of renal failure.
- Renal impairment; monitor renal function and consider discontinuation with progressive renal impairment.
- Pregnancy, second and third trimesters; use reduces fetal renal function and increases fetal and neonatal morbidity and death; discontinue as soon as possible when pregnancy is detected.
- Hyperuricemia may occur; frank gout may be precipitated.

Adverse Effects[1]

Adverse Reactions	Frequency
Dizziness	8.9%
Fatigue	2%
Hypotension	1.7%

Drug Interactions[1]

- Lithium
- NSAIDs

Dosage and Administration[1]

The initial dose is azilsartan 40 mg/chlorthalidone 12.5 mg orally once daily. The dose may be increased to 40 mg/25 mg after 2 to 4 weeks as needed to achieve blood pressure goals. The maximum recommended dose is 40 mg/25 mg once daily.

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH*
Azilsartan/ chlorthalidone	Edarbyclor	Takeda	40 mg/12.5 mg tablets	1 tablet QD	$ 83.10
			40 mg/25 mg tablets	1 tablet QD	$ 83.10
Azilsartan	Edarbi	Takeda	40 mg tablets	1 tablet QD	$ 81.00
Chlorthalidone	Generic	Mylan	25 mg tablets	1 tablet QD	$ 11.07

***Wholesale Acquisition Cost**

Conclusion

Edarbyclor® is a fixed-dose combination of an ARB (azilsartan) and a thiazide-like diuretic (chlorthalidone) that has demonstrated efficacy for the treatment of moderate or severe hypertension. Edarbyclor® has shown to be more effective than each azilsartan and chlorthalidone as monotherapy in patients with hypertension that requires a multiple drug regimen.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1. Product Information: Edarbyclor®, azilsartan medoxomil and chlorthalidone tablets. Takeda Pharmaceuticals America, Inc., Deerfield, IL, 12/2011.
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Date: May 2, 2012