



NDA 202331/S-011

**SUPPLEMENT APPROVAL**

Arbor Pharmaceuticals, LLC  
Attention: Brianna Warren  
Manager, Regulatory Affairs, Labeling  
6 Concourse Parkway  
Suite 1800  
Atlanta, GA 30328

Dear Ms. Warren:

Please refer to your Supplemental New Drug Application (sNDA) dated and received April 25, 2016, and your amendment dated October 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Edarbyclor (azilsartan kamedoxomil/chorthalidone) 40/12.5 mg and 40/25 mg Tablets.

This Prior Approval supplemental new drug application provides for labeling revised as follows (additions are shown as underlined text and deletions are shown as ~~striketrough~~ text):

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was added:

-----**RECENT MAJOR CHANGES**-----  
Contraindications (4) 04/2016

2. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following text was added:

- Do not coadminister aliskiren-containing products with Edarbi in patients with diabetes. (4)

3. Under **CONTRAINDICATIONS**, the following text was added:

Do not coadminister aliskiren-containing products with Edarbi in patients with diabetes  
[see *Drug Interactions* (7)].

4. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following bullets were added to the list:

- Nausea
- Syncope
- Loss of consciousness
- Rash
- Pruritus
- Angioedema

5. Under **CLINICAL PHARMACOLOGY/Mechanism of Action**, the following text was added to the first, second, and 6<sup>th</sup> paragraphs:

The active ingredients of Edarbyclor target two separate mechanisms involved in blood pressure regulation. ~~Azilsartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells. Chlorthalidone produces diuresis with increased excretion of sodium and chloride.~~

*Azilsartan medoxomil*

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzymes (ACE, kinase II). Angiotensin II is the principle pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Azilsartan medoxomil is an orally administered prodrug that is rapidly converted by esterases during absorption to the active moiety, azilsartan. Azilsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathway for angiotensin II synthesis.

*Chlorthalidone*

Chlorthalidone produces diuresis with increased excretion of sodium and chloride. The site of action appears to be the distal renal tubule (early convoluted part), inhibiting NaCl reabsorption (by antagonizing the Na<sup>+</sup>-Cl-cotransporter) and promoting Ca<sup>++</sup> reabsorption (by an unknown mechanism). The enhanced delivery of Na<sup>+</sup> and water to the cortical collecting tubule and/or the increased flow rate leads to increased secretion and elimination of K<sup>+</sup> and H<sup>+</sup> -the cortical diluting segment of the ascending limb of Henle's loop of the nephron. The diuretic effects of chlorthalidone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. Although the mechanism of action of chlorthalidone and related drugs is not wholly clear, sodium and water depletion appear to provide a basis for its antihypertensive effect.

6. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added/deleted from the first, second, sixth, seventh, eighth, and ninth paragraphs:

*Edarbyclor*

Following oral administration of Edarbyclor, peak plasma concentrations of azilsartan and chlorthalidone are reached at 3 and 1 hour, respectively. The rate (C<sub>max</sub> and T<sub>max</sub>) and extent (AUC) of absorption of azilsartan are similar when it is administered alone or with chlorthalidone. The extent (AUC) of absorption of chlorthalidone is similar when it is administered alone or with azilsartan medoxomil; however, the C<sub>max</sub> of chlorthalidone from Edarbyclor was 45-47% higher. ~~The elimination half-lives of azilsartan and chlorthalidone are approximately 12 hours and 45 hours, respectively.~~

There is no clinically significant effect of food on the bioavailability of azilsartan or chlorthalidone following administration of Edarbyclor.

*Azilsartan medoxomil*

*Absorption:* Azilsartan medoxomil is an orally administered prodrug that is rapidly hydrolyzed converted by esterases during absorption to the active moiety, azilsartan~~to azilsartan, the active metabolite, in the gastrointestinal tract during absorption.~~ Azilsartan medoxomil is not detected in plasma after oral administration. Dose proportionality in exposure was established for azilsartan in the azilsartan medoxomil dose range of 20 mg to 320 mg after single or multiple dosing.

The estimated absolute bioavailability of azilsartan following administration of azilsartan medoxomil is approximately 60%. After oral administration of azilsartan medoxomil, peak plasma concentrations ( $C_{max}$ ) of azilsartan are reached within 1.5 to 3 hours. Food does not affect the bioavailability of azilsartan.

#### *Distribution*

*Azilsartan medoxomil:* The volume of distribution of azilsartan is approximately 16L. Azilsartan is highly bound to human plasma proteins (>99%), mainly serum albumin. Protein binding is constant at azilsartan plasma concentrations well above the range achieved with recommended doses.

In rats, minimal azilsartan-associated radioactivity crossed the blood-brain barrier. Azilsartan passed across the placental barrier in pregnant rats and was distributed to the fetus.

*Chlorthalidone:* In whole blood, chlorthalidone is predominantly bound to erythrocyte carbonic anhydrase. In the plasma, approximately 75% of chlorthalidone is bound to plasma proteins, 58% of the drug being bound to albumin. Chlorthalidone crosses the placental barrier and passes into breast milk. When mothers were treated before and after birth with 50 mg chlorthalidone daily, chlorthalidone levels in fetal whole blood were around 15% of those found in maternal blood. Chlorthalidone concentrations in amniotic fluid and breast milk are approximately 4% of those found in maternal blood.

#### *Metabolism and Elimination*

*Azilsartan medoxomil:* Azilsartan medoxomil, when administered alone or in combination with chlorthalidone is eliminated from plasma with an elimination half-life of 11-13 hours. Azilsartan is metabolized to two primary metabolites. The major metabolite in plasma is formed by *O*-dealkylation, referred to as metabolite M-II, and the minor metabolite is formed by decarboxylation, referred to as metabolite M-I. Systemic exposures to the major and minor metabolites in humans were approximately 50% and less than 1% of azilsartan, respectively. M-I and M-II do not contribute to the pharmacologic activity of azilsartan medoxomil. The major enzyme responsible for azilsartan metabolism is CYP2C9.

Following an oral dose of  $^{14}\text{C}$ -labeled azilsartan medoxomil, approximately 55% of radioactivity was recovered in feces and approximately 42% in urine, with 15% of the dose excreted in urine as azilsartan. The elimination half-life of azilsartan is approximately 11 hours and renal clearance is approximately 2.3 mL/min. Steady-state levels of azilsartan are achieved within 5 days and no accumulation in plasma occurs with repeated once-daily dosing.

*Chlorthalidone:* Chlorthalidone when administered alone or in combination with azilsartan medoxomil is eliminated from plasma with an elimination half-life of 42-45

~~hours. The elimination half-life is unaltered following repeat dosing. The majority of an absorbed quantity of chlorthalidone is excreted by the kidneys with a mean renal clearance of 46 -70 mL/min. By contrast, metabolism and excretion via the liver and bile play a minor role in the elimination of the substance. Approximately 60 - 70% of chlorthalidone is excreted in the urine and feces within 120 hours, mainly in unchanged form. 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.~~

#### Special Populations

*Azilsartan medoxomil*: The effect of demographic and functional factors on the pharmacokinetics of azilsartan was studied in single and multiple dose studies. Pharmacokinetic measures indicating the magnitude of the effect on azilsartan are presented in Figure 2 as change relative to reference (test/reference).

### 7. Under NONCLINICAL TOXICOLOGY, the following text was added:

#### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No carcinogenicity, mutagenicity, or fertility studies have been conducted with the combination of azilsartan medoxomil and chlorthalidone or with chlorthalidone alone. However, these studies have been conducted for azilsartan medoxomil, azilsartan and M-II.

##### *Azilsartan medoxomil*

*Carcinogenesis*: Azilsartan medoxomil was not carcinogenic when assessed in 26-week transgenic (Tg.rasH2) mouse and 2-year rat studies. The highest doses tested (450 mg azilsartan medoxomil/kg/day in the mouse and 600 mg azilsartan medoxomil/kg/day in the rat) produced exposures to azilsartan that are 12 (mice) and 27 (rats) times the average exposure to azilsartan in humans given the maximum recommended human dose (MRHD, 80 mg azilsartan medoxomil/day). M-II was not carcinogenic when assessed in 26-week Tg.rasH2 mouse and 2-year rat studies. The highest doses tested (approximately 8000 mg M-II/kg/day (males) and 11,000 mg M-II/kg/day (females) in the mouse and 1000 mg M-II/kg/day (males) and up to 3000 mg M-II/kg/day (females) in the rat) produced exposures that are, on average, about 30 (mice) and 7 (rats) times the average exposure to M-II in humans at the MRHD.

*Mutagenesis*: Chlorthalidone demonstrated no potential for mutagenic effects at non-cytotoxic concentrations and is considered not to pose a mutagenic risk to humans.

Azilsartan medoxomil, azilsartan, and M-II were positive for structural aberrations in the Chinese Hamster Lung Cytogenic Assay. In this assay, structural chromosomal aberrations were observed with the prodrug, azilsartan medoxomil, without metabolic activation. The active moiety, azilsartan, was also positive in this assay both with and without metabolic activation. The major human metabolite, M-II was also positive in this assay during a 24-hr assay without metabolic activation.

Azilsartan medoxomil, azilsartan, and M-II were devoid of genotoxic potential in the Ames reverse mutation assay with *Salmonella typhimurium* and *Escherichia coli*, the *in vitro* Chinese Hamster Ovary Cell forward mutation assay, the *in vitro* mouse lymphoma (tk) gene mutation test, the *ex vivo* unscheduled DNA synthesis test, and the *in vivo* mouse and/or rat bone marrow micronucleus assay.

Impairment of Fertility: Chlorthalidone at a dose of 100 mg/kg had no effect on fertility in rats. There was no effect of azilsartan medoxomil on the fertility of male or female rats at oral doses of up to 1000 mg azilsartan medoxomil/kg/day [6000 mg/m<sup>2</sup> (approximately 122 times the MRHD of 80 mg azilsartan medoxomil/60 kg on a mg/m<sup>2</sup> basis)]. Fertility of rats also was unaffected at doses of up to 3000 mg M-II/kg/day.

### **13.2 Animal Toxicology and/or Pharmacology**

#### *Edarbyclor*

#### Repeat dose toxicity

The safety profiles of azilsartan medoxomil and chlorthalidone monotherapy have been individually established. To characterize the toxicological profile for Edarbyclor, a 13-week repeat-dose toxicity study was conducted in rats. The results of this study indicated that the combined administration of azilsartan medoxomil, M-II, and chlorthalidone resulted in increased exposures to chlorthalidone. Pharmacologically-mediated toxicity, including suppression of body weight gain and decreased food consumption in male rats, and increases in blood urea nitrogen in both sexes, was enhanced by coadministration of azilsartan medoxomil, M-II, and chlorthalidone. With the exception of these findings, there were no toxicologically synergistic effects in this study.

8. The revision date and version number were updated.

There are no other changes from the last approved package insert.

### **APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

#### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN, RAC  
Regulatory Project Manager for Safety  
(301) 796-3975

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, PharmD.  
Deputy Director for Safety  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
10/24/2016