CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202331Orig1s000

<u>OTHER REVIEW(S)</u>

RHPM Overview – AP action
NDA 202-331
Edarbyclor (azilsartan medoxomil and chlorthalidone) Tablets
40/12.5 and 40/25 mg

Sponsor:	Takeda Pharmaceuticals North America
Classification:	Standard
Submission Date:	February 24, 2011
Receipt Date:	February 24, 2011
User Fee Goal Date:	December 24, 2011

Background

Edarbyclor is an oral, fixed-dose combination tablet containing TAK-491 (azilsartan medoxomil) and chlorthalidone. TAK-491 is a pro-drug that is rapidly hydrolyzed to TAK-536 (azilsartan), an antagonist of the angiotensin II type I receptor. Chlorthalidone is a thiazide-like diuretic that has been marketed in the US since 1959. The monotherapy NDA for azilsartan medoxomil was approved on February 25, 2011 for the treatment of hypertension under the tradename Edarbi (NDA 200-796). The proposed indication for the fixed dose combination of TAK-491 and chlorthalidone is for the treatment of hypertension, including initial therapy. At the time of NDA submission, (b) (4) dosage strengths (b) (4) proposed: (b) (4) 40/12.5, (b) (4) and 40/25 mg. Clinical studies were conducted under IND 77,278.

In support of approval, the sponsor submitted efficacy and safety results from seven Phase 3 studies, in which 2358 subjects received TAK-491CLD and 819 subjects received TAK-491 coadministered with chlorthalidone. Of these, 4 studies were conducted with the FDC tablet (studies 302, 306, 301, and 308). The pivotal study, 491CLD-302, was an 8-week, randomized, double-blind, controlled, fixed-dose, factorial study that evaluated the efficacy and safety of TAK-491CLD relative to TAK-491 and chlorthalidone monotherapies. The other three FDC studies were designed to compare TAK-491CLD with active comparators. Supportive data from three coadministration studies (i.e.,TAK-491 plus chlorthalidone) were also resubmitted from the TAK-491 monotherapy program; these studies included a short-term, double-blind, randomized, placebo-controlled study and two long-term, open-label safety studies. Additionally, a TAK-491CLD Phase 3 randomized, active-controlled, 12-week study (491CLD-303) to evaluate the efficacy and safety of TAK-491CLD compared with the olmesartan medoxomil and HCTZ FDC, which was recently completed at the time of NDA submission, was also included.

An EOP1 meeting was held on 4-4-06. Pre-NDA meetings were cancelled because the Pre-NDA Meeting Preliminary Responses for the non-clinical and CMC sections (dated 9-9-10) and clinical and clinical pharmacology sections (dated 11-8-10) were sufficient.

Division Director's Memo

Dr. Stockbridge's 12-16-11 memo "conveys the Division's recommendation to issue an Approval letter for Edarbyclor for hypertension." See memo in DAARTS.

Cross-Discipline Team Leader Review

In her 11-10-11 review, Dr. Targum recommended approval. See review in DAARTS.

Clinical Review

In his 11-22-11 addendum to his 10-3-11 review, Dr. U concluded the following:

> My review of the sponsor's response does not reveal any mitigating information to require a change in recommendation of regulatory action from its current recommendation for "**approval**" status apart from appropriate amendments to the proposed label to the claim of efficacy in Black subjects, and minor changes to the label as discussed above.

Statistical Review
In her 12-15-11 review, Dr. Zhang "found the proposed labeling graphs acceptable."

In her 11-28-11 review, Dr. Zhang concluded that "The estimated probabilities of achieving blood pressure goals based on logistic regression modeling appeared to be adequate. The graphs adequately represent the study data and support for the approval of initial therapy indication.

In her 8-6-11 review, Dr. Zhang wrote the following:

> **Conclusions and Recommendations**
> This review includes 4 placebo-controlled studies that compared the fixed-dose combination tablet TAK-491CLD with monotherapies or active-controls (OLM/HCTZ, or TAK-491+HCTZ). Although missing data remains a concern for this application, the consistent results in various sensitivity analyses and in different blood pressure measurements offer certain assurance that missing data would unlikely affect the conclusion of the studies. The fixed-dose combination tablet TAK-491CLD is effective in treating moderate to severe essential hypertension.

Clinical Pharmacology Review
In her 8-22-11 review, Dr. Menon-Andersen wrote the following:

> **Recommendation**
> The Office of Clinical Pharmacology (OCP/DCP1) reviewed original NDA 202-331, and recommends approval from a clinical pharmacology perspective.

Pharmacology review
In his 7-18-11 review, Dr. Gatti indicated that the NDA was approvable. See review in DAARTS.

ONDQA Biopharmaceutics review
In his review dated 10-24-11, Dr. Chen wrote the following:

> **RECOMMENDATION:**
> ONDQA-Biopharmaceutics had evaluated the overall information supporting the approval of this submission. From the Biopharmaceutics perspective, this NDA is recommended for approval with a PMC as agreed upon in the 10/13/11 teleconference with the Applicant. The following Post Marketing Commitment comment needs to be included in the Approval Letter or sent to the Applicant.
>
> > **Post Marketing Commitment:**
> > As agreed upon in the teleconference held on October 13, 2001, you commit to provide a Supplement to the NDA within 14 months of approval date. This supplement should include the dissolution data gathered for all strengths of azilsartan medoxomil and chlorthalidone from the batches manufactured during the first year following approval date. If the Stage 2 testing is observed to be (b) (4) then a justification will be presented to support re-evaluation of the dissolution acceptance criteria for all strengths of both azilsartan medoxomil and chlorthalidone. If the Stage 2 testing is (b) (4) then the current interim acceptance criteria will remain and will be set as the final regulatory criteria for your product.

See also PMR/PMC Development Template dated 11-22-11 in DAARTS.

Chemistry review
In his review #2 dated 11-1-11, Dr. Shiromani wrote the following:

Recommendation and Conclusion on Approvability
The applicant has provided adequate responses to the FDA CMC IR letter sent on 27-Jun-2011. Additionally, the ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS (10-24-2011); revised drug product dissolution specifications are recommended therein. They conclude that this NDA is recommended for approval with a Post Marketing Commitment to be included in the Approval Letter, which the applicant has agreed to in their Supplement # 25; this PMC is included in their review. There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective with the inclusion of the above PMC.

See also his Chemistry review dated 7-11-11.

Environmental Assessment
The sponsor submitted an Environmental Assessment (EA) pursuant to 21 CFR Part 25, which was found to be acceptable. See Chemistry reviews.

EER Report
The Office of Compliance issued an Overall Recommendation of "Acceptable" on 5-20-11 (D. Smith); see Chemisry reviews.

Safety Update
Page 104 of Dr. U's clinical review dated 10-3-11 states the following:

7.7 Additional Submissions / Safety Issues
On 23-Jun-2011, the sponsor submitted a 120-Day Periodic Safety Update Report which includes (i) a summary of the safety and efficacy information contained in the Study 303 CSR, (ii) additional safety data obtained from the ongoing open-label Study 308, and (iii) the safety data from the recently completed phase 1 bioavailability (BA) Study 106 (which compared the relative bioavailability of TAK-491 CLD FDC tablets compared with co-administration of individual TAK-491 tablets and CLD tablets sourced in the European Union). These data are integrated into the clinical safety review in section 7.1 to 7.5 above.

Financial Disclosure
Page 17 of Dr. U's clinical review dated 10-3-11 states the following:

The sponsor submitted financial disclosure information for clinical investigators in Studies 302, 301, 306 and 009; none of the investigators had disclosable financial interests. The sponsor stated that no financial disclosure information would be provided for open-label studies and Phase I studies. This arrangement had been agreed to by the Division per the pre-NDA meeting minutes dated 02-Nov-2010.

Office of Scientific Investigations
In her Clinical Inspection Summary dated 10-13-11, Dr. Gershon wrote the following:

In general, inspection of the four clinical investigator sites (Lefebrvre, Roth, Dewan, Lopez) revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. Only minor regulatory violations were found at two sites (Dr. GiGi Lefebrvre and Dr. Danilo Lopez), and they received a VAI classification. The other two sites (Roth and Dewan) received NAI classifications.

OSI conducted a CRO inspection of (b) (4) and included a Part 11 Clinical Inspectional assignment to ensure CRO and Sponsor understanding and compliance with 21 CRF 21 Part 11 regulations and guidance (electronic records), in regards to use of the ABPM device, and

transmission of 24-hour BP readings to the Sponsor. No regulatory violations were noted during this inspection.

With the exception of the items noted above, the study appears to have been conducted adequately, and the data generated by these sites may be used in support of the respective indication.

Pediatrics
The sponsor requested a waiver from the pediatric requirement and the Division agreed. In an email dated 10-13-11, G. Greenley stated the following:

> This email serves as confirmation of the review for Edarbyclor (azilsartan medoxomil plus chlorthlalidone) conducted by the PeRC PREA Subcommittee on July 13, 2011.
>
> The Division presented a full waiver in pediatric patients for the indication of treatment of hypertension because the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients.
>
> The PeRC agreed with the Division to grant a full waiver for this product.

See also the pediatric record in DAARTS.

Labeling
The original submission contains proposed draft labeling for the package insert (PI), patient package insert (PPI), and container and carton labeling in SPL and PLR format where appropriate. Updated labeling was submitted on 6-23-11 as part of the Safety Update.

DMPP provided comments on the proposed PPI in a review dated 11-8-11.

OPDP provided comments on the proposed PI and PPI in a review dated 11-10-11.

DMEPA found the revised proposed container and carton labeling submitted on 11-29-11 to be acceptable in their review dated 12-9-11. See also 8-2-11 review regarding the previously submitted labeling.

The Division's labeling comments were sent to the sponsor on 11-25-11, 12-1-11 and 12-9-11. Labeling meetings were held with the sponsor on 12-1-11 and 12-12-11 (telecon). The final draft labeling (submitted by the sponsor on 12-13-11) was agreed upon by the Division on 12-16-11.

Tradename Review
DMEPA concluded that the proposed proprietary name "Edarbyclor" was acceptable in their reviews dated 12-5-11 (final) and 7-12-11 (original).

Safety Discussion
A Safety Discussion was held as part of the Wrap-Up Meeting on 11-3-11 with OSE-DPV.

User Fee
The user fee for this application was paid in full (User Fee ID# PD3011109).

505(b)(2) Clearance
Per a 11-21-11 email from Beth Duvall-Miller of OND, this NDA is cleared for action from a 505(b)(2) perspective.

RPM Summary

An Approval (AP) Letter based on the agreed-upon labeling text will be drafted for Dr. Stockbridge's signature. The AP Letter will include a postmarketing commitment (see ONDQA Biopharmaceutics and Chemistry reviews, and the PMR/PMC Development Template).

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
12-20-11

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QUYNH M NGUYEN
12/20/2011

SEALD Director Sign-Off Memo and Labeling Review

Product Trade Name (Non-Propriety Name)	**EDARBYCLOR (azilsartan medoxomil and chlorthalidone)**
Application Number/Supplement Number	NDA 202331/S-1
Type of Application	Original NDA
Indication	Treatment of Hypertension
Applicant	Takeda Pharmaceuticals
Office/Division	ODEI/DCRP
Division Project Manager	Quynh Nguyen
Submission Date	February 24, 2011
PDUFA Goal Date	December 24, 2011
SEALD Review Date	December 15, 2011
SEALD Labeling Reviewers	Perry Mackrill and Eric Brodsky
SEALD Director	Laurie Burke

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state “None”)
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

Reference ID: 3059851

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)**."

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

Reference ID: 3059851

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**
  - ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

    http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**
  - ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
  - ☐ All contraindications listed in the FPI must also be listed in HL.
  - ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**
  - ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (<u>insert name of manufacturer</u>) at (<u>insert manufacturer’s phone number</u>) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**
  - ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**.

- **Revision Date**
  - ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Reference ID: 3059851

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

Reference ID: 3059851

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for "peds only" indications) are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling …

    (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Reference ID: 3059851

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/s/

ERIC R BRODSKY
12/16/2011

LAURIE B BURKE
12/16/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 202331	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Edarbyclor Established/Proper Name: azilsartan medoxomil plus chlorthalidone Dosage Form: Tablet Strengths: 40/12.5 and 40/25 mg		
Applicant: Takeda Pharmaceuticals North America		
Date of Receipt: 2-24-11		
PDUFA Goal Date: 12-24-11	Action Goal Date (if different):	
Proposed Indication(s): Treatment of hypertension, including initial therapy.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Reference ID: 3058777

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Hygroton (NDA 12-283)	Clinical pharmacology and nonclinical evaluations of chlorthalidone

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Clinical pharmacology studies were completed in support of the TAK-491CLD NDA as described in Module 2.7.2. These included a bioavailability study that compared the TAK-491CLD FDC to the individual azilsartan medoxomil and chlorthalidone monotherapy tablets. The chlorthalidone monotherapy tablets utilized were manufactured by Mylan (ANDA 086831), which is therapeutically equivalent to Hygroton (NDA 012283), the reference listed product. In addition, population pharmacokinetics of each component of TAK-491CLD FDC were characterized in subjects with hypertension in the Phase 3 study TAK-491CLD-302. Literature support is also provided for the clinical pharmacology of chlorthalidone in Module 2.7.2.

For completeness, TGRD also references the Agency's previous clinical pharmacology evaluation of chlorthalidone in the Hygroton NDA 012283.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

Reference ID: 3058777

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

Reference ID: 3058777

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Hygroton	NDA 12-283	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Reference ID: 3058777

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Hygroton (NDA 12-283)

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a fixed-dose combination product of azilsartan medoxomil and chlorthalidone.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

Reference ID: 3058777

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Reference ID: 3058777

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

Reference ID: 3058777

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Reference ID: 3058777

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/s/

QUYNH M NGUYEN
12/15/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	December 9, 2011
Reviewer:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Irene Z. Chan, Pharm.D., Team Leader Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
Drug Name:	Edarbyclor (Azilsartan Medoxomil and Chlorthalidone) Tablets, 40 mg/12.5 mg and 40 mg/25 mg
Application Type/Number:	NDA 202331
Applicant/sponsor:	Takeda Pharmaceuticals
OSE RCM #:	2011-704-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Edarbyclor (Azilsartan Medoxomil and Chlorthalidone) Tablets submitted in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments to the Applicant in OSE Review #2011-704, dated August 3, 2011.

2 MATERIAL REVIEWED

The revised container label and carton labeling submitted to the FDA on July 12, 2011, (See Appendices A and B) and OSE Review #2011-704, dated May 5, 2011, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels and carton labeling submitted on November 29, 2011, address all of DMEPA's concerns. Thus, we have no further recommendations on the container labels and carton labeling.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Nina Phoung Ton at 301-796-1648.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3056538

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/s/

YELENA L MASLOV
12/09/2011

CAROL A HOLQUIST
12/12/2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name:	NDA 202-331/Edarbyclor (azilsartan medoxomil plus chlorthalidone) Tablets
PMR/PMC Description:	Provide a supplement including the *in vitro* dissolution data gathered for all strengths of azilsartan medoxomil and chlorthalidone from the batches manufactured during the first year following approval date. If the dissolution Stage 2 testing is observed to be (b) (4) provide a justification to support the re-evaluation of the dissolution acceptance criteria for all strengths of both azilsartan medoxomil and chlorthalidone.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	
	Study/Trial Completion:	
	Final Report Submission:	12/24/2012
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3048266

This PMC is to allow the Applicant to generate additional *in vitro* dissolution data and to set the final dissolution acceptance criteria post approval.

The following dissolution criteria are recommended on an interim basis.

a. **Azilsartan medoxomil:**
Q= (b) (4) at 30 min for (b) (4) 40/12.5, 40/25 mg strengths.
(b) (4)

b. **Chlorthalidone:**
Q= (b) (4) at 15 min for (b) (4) 40/12.5, 40/25 mg strengths.
(b) (4)

The PMC will provide post marketing dissolution acceptance criteria and allow the Agency to assess the adequacy of the acceptance criteria and require further modifications if necessary.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Reference ID: 3048266

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

It was agree upon that the Applicant would generate more *in vitro* dissolution data and submit the dissolution results and proposed dissolution acceptance criteria for discussion with the Agency within 14 months of approval date.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Additional *in vitro* dissolution testing

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?

Reference ID: 3048266

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3048266

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/s/

TIEN MIEN CHEN
11/22/2011

ANGELICA DORANTES
11/22/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: November 10, 2011

To: Quynh Nguyen
Regulatory Project Manager
Division of Cardio-Renal Products

From: Emily Baker, Regulatory Review Officer
Zarna Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Drug: Edarbyclor (azilsartan medoxomil and chlorthalidone) tablets**
NDA: 202331

OPDP has reviewed the proposed Package Insert (PI) and Patient Labeling (PPI) submitted for consult on April 27, 2011, for Edarbyclor (azilsartan medoxomil and chlorthalidone) tablets. Our comments are provided directly on the attached proposed PI and PPI (Division of Medical Policy Programs' (DMPP) version dated October 8, 2011).

OPDP reviewed the comments on the proposed PPI from DMPP dated October 8, 2011, and we have no further comments on the proposed attached PPI.

Our comments are based on the proposed labeling circulated to the review team on October 26, 2011.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the comments for the PI, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

If you have any questions on the comments for the PPI, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

EMILY K BAKER
11/10/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	November 7, 2011
To:	Norman Stockbridge, MD, PhD, Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling (Patient Package Insert)
Drug Name (established name):	EDARBYCLOR (azilsartan medoxomil and chlorthalidone)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 202-331
Applicant:	Takeda Pharmaceuticals North America, Inc.
OSE RCM #:	2011-1338

1 INTRODUCTION

This review is written in response to a request by the Division of Cardiovascular and Renal Products (DCRP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for EDARBYCLOR (azilsartan medoxomil and chlorthalidone) tablets.

The purpose of the Applicant's submission is to seek approval of original New Drug Application (NDA) 202-331. The proposed indication is for the treatment of hypertension, to lower blood pressure: in patients not adequately controlled with monotherapy; as initial therapy in a patient who is likely to need multiple drugs to help achieve blood pressure goals.

2 MATERIAL REVIEWED

- Draft EDARBYCLOR (azilsartan medoxomil and chlorthalidone) tablets Patient Package Insert (PPI) received on June 23, 2011.
- Draft EDARBYCLOR (azilsartan medoxomil and chlorthalidone) tablets Prescribing Information (PI) received June 23, 2001, revised by the Review Division throughout the current review cycle and received by the Patient Labeling Team on October 26, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
11/07/2011

BARBARA A FULLER
11/07/2011

LASHAWN M GRIFFITHS
11/08/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 18, 2011

TO: Quynh Nguyen, Regulatory Project Manager
Khin Maung U, Medical Officer
Shari Targum, Clinical Team Leader
Division of Cardio-Renal Products (DCRP)

FROM: Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-331

APPLICANT: Takeda Global Research & Development, Inc.

DRUG: Edarbychlor (azilsartan medoxomil + chlorthalidone fixed dose combination)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of moderate to severe essential hypertension

CONSULTATION REQUEST DATE: April 7, 2011

DIVISION ACTION GOAL DATE: December 20, 2011

PDUFA DATE: December 24, 2011

I. BACKGROUND:

NDA 202-331 was submitted by Takeda Pharmaceuticals North America, Inc. for the proposed use of a fixed dose combination (FDC) of azilsartan medoxomil plus chlorthalidone (TAK-491CLD) for treatment of moderate to severe essential hypertension. The data supporting approval for this FDC came from four phase III studies: TAK-491CLD **302, 301**, **306 and 308**. Azilsartan medoxomil is a renin-angiotensin-aldosterone system (RAAS) blocker, and chlorthalidone is a diuretic.

Pivotal study TAK-491CLD-**302** was a randomized, double-blind, factorial study design, comparing the antihypertensive effect of TAK-491 CLD with TAK-491 (azilsartan medoxomil) monotherapy and chlorthalidone monotherapy after 8 weeks of treatment. The other 3 supportive studies included two short-term, randomized, double-blind, comparator controlled studies, TAK 491CLD-**306** and TAK 491CLD-**301**, and one 52-week, randomized, open-label**,** comparator-controlled safety study, 491CLD-**308**. Study 491CLD-**306** compared TAK-491CLD against co-administration of TAK-491 plus diuretic hydrochlorothiazide (HCTZ), whereas Study 491CLD-**301** and Study 491CLD-**308** used olmesartan medoxomil plus HCTZ (OLM/HCTZ) for a comparator. The long-term, 52-week open-label safety study (TAK-491CLD- **308)** is ongoing.

The following two protocols were audited during clinical site inspections for this NDA:

1) TAK-491CLD- **302:** A Phase 3, Double-blind, Randomized, Factorial, Efficacy and Safety Study of TAK-491 Plus Chlorthalidone Fixed-Dose Combination in Subjects with Moderate to Severe Hypertension

Design and Methodology:

Subjects with moderate to severe essential hypertension systolic blood pressure (SBP) between 160 and 190 mm Hg, inclusive), were enrolled. Subjects were randomized to receive 1 of 11 possible dosing combinations of azilsartan medoxomil, chlorthalidone and placebo over an 8-week period. The total duration of the study was approximately 13 weeks, including a 21 to 28 day washout of previous antihypertensive agents. There were between 147 to 162 subjects per treatment group. Subjects made 12 visits to the clinic. Each subject was also contacted by telephone 14 days after last dose of study drug for a follow-up assessment.

Primary Efficacy:
The primary efficacy variable for Study 302 was the change from Baseline to Week 8 in trough (22 to 24 hour interval after dosing) SBP by Ambulatory Blood Pressure Monitoring (ABPM)

device worn by the subject. Evaluation of the response in Black subjects was a key secondary objective of the factorial study.

Measurement of 24-hour ABPM was conducted 3 times during the study. The Baseline recording was performed immediately after dosing on the last day of the Placebo Run-In Period; a second ABPM recording was performed after administration of study drug at Week 4, and the final ABPM was performed starting immediately after administration of the last dose of study medication at the Week 8 Visit.

Conclusions from Study 302:
The following was observed:

- Each of the 6 TAK-491 CLD FDC strengths lowered trough SBP and diastolic blood pressure (DBP) more effectively than the component monotherapy agents by both ABPM and clinic blood pressure (BP) measurements done manually.
- Similar magnitudes of BP reduction were observed in nearly all subgroups, including Black subjects.
- Total numbers of adverse events and discontinuations due to adverse events were dose-related and more frequent in the TAK-491CLD FDC groups, compared to the monotherapy groups, Serious Adverse Events (SAEs) were uncommon in all treatment groups.

2) TAK-491CLD**- 301:** A Phase 3, Double-Blind, Randomized, Effcacy and Safety Study Comparing the TAK-491 Plus Chlorthalidone Fixed-Dose Combination vs. Benicar HCTZ (Olmesartan Medoxomil-Hydrochlorothiazide) in Subjects with Moderate to Severe Essential Hypertension
Hypertension

Design and Methodology:

Subjects with moderate to severe essential hypertension (SBP between 160 and 190 mm Hg, inclusive) were enrolled into this Phase III, double-blind, randomized, parallel-group, 8-week efficacy and safety study comparing TAK-491CLD versus OLM/HCTZ. Subjects were randomized to 8 weeks of treatment with one of the following treatment regimens: TAK-491CLD 20 mg/12. 5mg; TAK-491CLD 40 mg/12.5 mg; or OLM/HCTZ 20mg/12.5 mg. For subjects who did not achieve their target SBP and DBP targets by Week 4, study drug was titrated to a higher dose. Subjects who achieved both BP targets by Week 4 continued to receive their starting dose for the remainder of the study. Sitting and standing trough clinic BP readings and pulse measurements were measured in the clinic throughout the study. A 24-hour ABPM was conducted 3 times – at baseline, at an interim Week 4 visit, and at the final Week 8 visit. The total duration of the study was approximately 12 weeks, and subjects made at least 11 visits to the clinic.

Primary efficacy:
The primary efficacy endpoint for Study 301 was a change from Baseline to Week 8 in trough, sitting, clinic SBP. Secondary endpoints included change from Baseline to Week 4 in trough, sitting, clinic SBP and change from baseline to Weeks 4 and 8 in various ABPM parameters, as

listed in the protocol.

Conclusions from Study **301**:
The following was observed:

- TAK-491 CLD treatment resulted in greater BP reduction than OLM/HCTZ.
- Both TAK-491 CLD and OLM/HCTZ were well tolerated. SAEs were uncommon in all treatment groups. However, discontinuations due to AEs were dose-dependent and more frequent in the TAK-491 CLD groups.

RATIONALE FOR CLINICAL SITE SELECTION:

TAK-491CLD is a fixed-dose combination oral product with a proposed indication of reduction of moderate to severe hypertension. The clinical sites selected for inspection were chosen using a combination of OSI's Risk Based Model for Site Selection and choice of sites of particular concern identified by the review division. For the pivotal Study TAK-491CLD **302**, 3 sites were selected for inspection (Lefebrvre, Roth, Dewan), and for TAK-491CLD **Study 301**, one site was chosen for inspection (Lopez). In general, these sites enrolled relatively large number of patients, showed large effect size (in terms of mmHg reduction in SBP, compared to baseline and/or compared to placebo), and had many discontinuation(s), adverse events, and protocol violations.

II. RESULTS (by Site):

Site #/Name of CI/CRO	**Protocol #/# of Subjects**	**Inspection Dates**	**Final Classification**
Site #3019 GiGi Lefebrvre 4751 66th St North St Petersburg, FL 33907	TAK-491CLD **302** 43 subjects	06/1 – 06/15/11	VAI
Site #3026 Eli Roth 2230 Auburn Ave, Level B Cincinnati, OH 45239	TAK-491CLD **302** 36 subjects	06/07 – 06/10/11	NAI
Site #3042 Meera Dewan 11912 Elm St, Suite 26 Omaha, NE 68114	TAK-491CLD **302** 38 subjects	06/07- 06/10/11	Pending: Preliminary classification = NAI
Site #2032 Danilo Lopez 333 West 41st St, Suite 514 Miami Beach, FL	TAK-491CLD **301** 50 subjects	06/09 – 28/2011	VAI

(b) (4)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **GiGi Lefebrvre, M.D.**
   4751 66th Street North,
   St. Petersburg, FL 33907

a. What was inspected: The inspection audited Protocol TAK-491CLD-302 using the Compliance Program (CP) for Clinical Investigators 7348.811. This site screened 149 subjects, and enrolled 43 subjects (106 screen failures). Six subjects withdrew early (reasons not provided in EIR), and 37 subjects completed the study. The inspection reviewed informed consent documents (ICD) for all enrolled subjects, and reported no issues or discrepancies. The inspection performed an in-depth review of 30 of 43 subject records (70%), that included inclusion and exclusion criteria, concomitant medications, laboratory worksheets and documentation, clinic (manual) BP readings, dosing schedules, ABPM device training, adverse event reporting, and drug accountability compliance. The inspection cross-checked data from the Sponsor with information in the source records to ensure consistency. The inspection also cross-checked source documents with information entered into the eCRF for 20 subjects. The observations noted were based on the Form FDA 483 and the EIR with supporting exhibits.

b. General Observations/Commetary: The inspection reviewed the ICD for all enrolled subjects (43), and reported no discrepancies. At the conclusion of the inspection a multi-part, one observation Form FDA 483 was issued to Dr. Lefebvre for failure to follow the investigational plan. Specific findings were as follows:

1) Manual BP readings recorded on worksheets did not match the e-CRF for 3 subjects:

a. For Subject 116 at Visit 7 on 11/5/2009, the SBP was documented in source records as 156/86, but entered into the eCRF as 154/86;
b. For Subject 107, at Visit 4 on 10/6/09, the SBP was documented in source records as 160/102, but entered into the eCRF as 160/107;
c. For Subject 008, at Visit 11 on 6/24/2009, the SBP was documented in source records as 126/90, but entered into the eCRF as 136/90.

OSI Reviewer Comment: These discrepancies are relatively minor and appear to be isolated occurrences; therefore, it seems unlikely that they would significantly impact efficacy or safety analyses.

2) Subject 093 was reported as taking Meloxicam 7.5 mg BID from 9/17 – 10/13/09, for arthritic pain, whereas the protocol allows the use of NSAIDs up to 3 doses per

week. However, this was reported to the Sponsor as a protocol deviation, and the subject was informed of prohibited use of NSAIDS as per protocol, and agreed to use daily as needed for < 3 weeks.

3) Manual BP readings were not re-taken for 6 subjects, as per protocol Section 9.1.5, which states that when diastolic BP differed by > 5 mm Hg or when SBP differed by > 8 mm Hg for any 3 measurements, a second set of BP readings should be taken. These findings were not reported in the NDA as protocol deviations. However, Takeda monitoring reports document that the site was counseled on proper procedures regarding repeating elevated BP readings.

OSI Reviewer Comment: Review of the BP discrepancies reveal that the DBP readings differed by 6 mm Hg for 6 subjects, and that no signed protocol deviation forms were received. However, these BP differences are relatively minor (6 mm Hg versus 5 mm Hg). In addition, the study was an 8-week study, and these BP measurements occurred during single Visits 2, 3, 5 and 8 for 6 subjects. Given the sporadic nature of the violation, it does not appear that any attempt to systematically alter data occurred, and it seems unlikely that these protocol deviations would significantly impact NDA analyses.

4) BP readings were not always taken at trough level, as required by the protocol. The inspection provided 1 example for Subject 147 and 3 examples for Subject 114. The protocol states that dosing is once per day in the morning, and BPs should be measured in the morning approximately 24 hours after the previous day's dose. The examples are as follows:

i) On 4/6/10 at Visit 3, Subject 147 took study medication at 10 am and had BP measured between 11:18–11:24 am that same morning;

ii) On 10/18/09, Subject 114 took study drug at 10:15 pm, had BP measured at 8:43 am the following morning (10/19/09), and was re-dosed at 8:54 am in clinic on the same day.

iii) On 10/26/09, Subject 114 took study drug at 7:00 pm, was re-dosed at 8:35 am on 10/27/09 in the clinic, and had BP measured at 9:20 am the same morning;

iv) On 11/16/09, Subject 114 took study medication at 10:30 pm and had BP taken between 9:07-9:13 am the next morning (11/17/09), then was re-dosed at 9:54 am the same day.

OSI Reviewer Comment: The review division may wish to consider whether the timing of the BP assessments in Subject 114 would have a significant effect on the efficacy data reported for this subject.

Additionally, observations from the Establishment Inspection Report included that according to the protocol, in-clinic drug administration time was to be at 8:00 am ± 2 hours, but that for a majority of subject charts reviewed, the site did not always take

clinic BP measurements "before 10:00 am". According to Dr. Lefebvre, this was due to subject non-compliance with dose time administrations or keeping appointment times. OSI considers Dr. Lefebvre's response as adequate.

c. **Assessment of data integrity**: Examples of the clinical investigator's failure to adequately follow the protocol were identified during the inspection, which constitute regulatory violations. The examples, however, appear to be limited and sporadic in nature and there is no evidence to suggest errors occurred in a systemic manner with intent to alter study outcome. Dr. Lefebvre responded to the Form FDA 483, Inspectional Observations in a letter dated June 21, 2011. OSI considers her responses and plans to implement corrective actions to be adequate. With the exception of items noted above, the study appears to have been conducted adequately, and, the data generated by this site may be used in support of the respective indication.

2. **Eli Roth, M.D.**
   2230 Auburn Ave. Level B
   Cincinnati, Ohio 45239

a. **What was inspected**: The inspection audited Protocol TAK-491CLD-302 using the CP for Clinical Investigators 7348.811. At this site, a total of 79 subjects were screened and 36 subjects enrolled into the study. Thirty-three (33) subjects completed the study, and 3 subjects discontinued or withdrew. No serious adverse events were reported at this site.

The inspection did a review of all enrolled subject's Informed Consent Documents (ICD) and found no discrepancies. The inspection conducted an in-depth review of records for 18 enrolled subjects (50% of enrolled subjects), and ensured consistency between source documents (medical history, efficacy endpoints, protocol deviations, adverse events) and the sponsor's data listings. The observations noted were based on the EIR with supporting exhibits.

b. General observations/commentary: The inspection reported no discrepancies in the informed consent process and documentation. The inspection reported that one adverse event (Subject 006 - worsening osteoarthritis) was missing from the adverse event listings, and two medications (Percodan – Subject 106 and Nicoderm Patch - Subject 012) were missing from the concomitant medication listings.

The primary efficacy endpoint was a change from Baseline to Week 8 in trough SBP (22 to 24 hours after drug administration) as measured by the ABPM device. The inspection could not verify this data at the site because this data had been directly transmitted (electronically) from the ABPM device to (b) (4) a CRO. The inspection verified that the site received adequate training on use of the ABPM device and provided instructions for use to the patient throughout the study. OSI conducted an inspection of (b) (4) from August 1 through August 4, 2011 to verify primary efficacy data and compliance with Part 11 regulations, August 1-4, 2011 (see Section 5 below).

The inspection reviewed key secondary endpoints as measured during clinic visits, using a manual BP measuring device. This data was accurate and verifiable with data listings.

No major regulatory violations were found during the inspection at this site, and a Form FDA 483 was not issued.

c. Assessment of data integrity: In general, the study was conducted adequately and the data generated by this site appear acceptable in support of the respective indication.

3. **Meera Dewan, M.D. (STUDY 302)**
11912 Elm Street, Suite 26, Omaha, NE 68114

a. **What was inspected**: The inspection was conducted 6/7/ – 6/9/2011, and audited Protocol TAK-491CLD **302;** the inspection used the CP for Clinical Investigators 7348.811. At this site, a total of 80 subjects were screened, and 38 subjects randomized. A total of 33 subjects completed the study at this site. The inspection conducted a 100% review of informed consent documents for the 38 enrolled subjects, and reviewed and verified 11 subject charts (~ 30%) for the following areas: inclusion and exclusion criteria; adverse events; concomitant medications; drug accountability records, clinic visits, and laboratory worksheets. The inspection verified that all adverse events documented in the subject's clinic notes, and other verifiable data, were consistent with the sponsor's data listings. The observations noted are based on communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: The inspection reported there was no evidence of underreporting of adverse events, and no discrepancies between the sponsor's data listings and source documentation with respect to protocol deviations, or other verifiable data.

The field investigator noted that the 24-hour BP measurements from the ABPM device were not verifiable because this data was not maintained at the site. However, the field investigator reported that all *manual* BP measurements taken during clinic visits were consistent with data recorded in source documents. No FDA-483 was issued during the inspection.

Although no regulatory violations were noted, several discussions took place with the clinical investigator during the inspection. These included:

i. Source documents were sometimes difficult to read;
ii. Inadequate documentation presented that thermometers used in the study drug storage room was calibrated; this finding does not appear significant, and there is no evidence to suggest that the thermometers did not reflect accurate measurements.
iii. Keys used to lock study drug cabinets were stored in a general area

(clinic drawer) to which anyone had access.

OSI Reviewer Comments: These were general administrative issues, were not regulatory violations, and did not impact the overall reliability of the data.

c. **Assessment of data integrity**: There were no significant regulatory violations observed during the inspection, and the data at this site may be considered reliable in support of the NDA.

4. Danilo Lopez, MD
333 West 41st Street, Suite 514
Miami Beach FL 33140

a. **What was inspected**: This inspection took place 06/09 – 06/28/2011, and audited Protocol TAK-491CLD **301.** During the inspection, the following records were audited: source documents for 25 of 50 subjects for organization, completeness, and legibility; comparison of source documents with case report forms and data listings from the sponsor; assessment of inclusion and exclusion criteria to confirm eligibility; informed consent documents; assessments of adverse events; review of drug accountability records. The inspection reviewed monitoring logs and collected copies of monitoring reports (performed by Takeda). The inspection also gathered the instruction manual for use of the ABPM device. The observations noted were based on the Form FDA 483 and the EIR with supporting exhibits.

b. **General observations/commentary**: The inspection reported the following:

- all subjects were correctly evaluated according to inclusion and exclusion criteria;
- informed consent documents were properly obtained for all subjects prior to enrollment;
- adverse events were assessed and correctly reported;
- no discrepancies were noted between source records and CRFs;
- no discrepancies were noted in drug accountability records;
- monitoring was well done;
- drug storage, inventory and dispensation of study medication was done correctly.

During the inspection, the following deficiencies were noted related to failure to conduct the study according to the investigational plan (21 CFR 312.60). An FDA 483 was issued for the following:

- Subject 047 was enrolled at Visit 5 on October 28, 2009, even though an ECG on that date revealed a silent myocardial infarction had occurred between Visit 3 (washout period) and Visit 5 (beginning of treatment period). The MI was reported as having occurred 7 days prior on October 21, 2009. A protocol deviation (PD)

report had been filed, in which the Study Coordinator documented it was in the best interests for this subject to continue in the study since he had no medical insurance. The PD form was signed by Dr. Lopez. A signed sponsor consultation form was obtained, according to the sponsor's data listings. A recent MI (within the last 6 months) was a protocol violation. There is no evidence that this subject/patient was adversely impacted as a result of participation in the study.

- Subject 008 had a washout period of 19 days of Lisinopril, even though the protocol required a washout period of 21 days. A protocol deviation report was on file and submitted to the NDA.
- Laboratory test results were missing for several subjects -
  - Subject 003 HbA1C lab test at Visit 1 (screening visit) was missing. However, a protocol deviation record was on file.
  - Subject 003 chemistry panel II laboratory test at Week 6 (Visit 9) was missing;
  - Subject 007 clinic notes documented that subject began taking new concomitant medication at Visit 9 (Week 6), whereas the concomitant medication log of 8/4/2009 did not document this new medication;
  - The source worksheet for Subject 072 was missing a standing pulse measurement at Visit 6 (Week 2), and Subject 001 source worksheet was missing a weight measurement at Visit 6 (Week 2) and Visit 7 (Week 4) as required by the protocol.

OSI Reviewer Comments: *the above deficiencies are isolated occurrences, and unlikely to impact data integrity.*

c. **Assessment of data integrity**: Although some regulatory violations were noted, they appear to be isolated occurrences and minor in nature and do not appear to affect the overall integrity of the data at this site. OSI recommends the data as acceptable in support of the NDA.

5. (b) (4)

a. **What was inspected**: This inspection was conducted according to CP 7347.810 for Sponsors, Contract Research Organizations, and Monitors. A Part 11 Clinical Inspectional assignment was included with the inspection, to ensure CRO and Sponsor understanding and compliance with 21 CRF 21 Part 11 regulations and guidance (electronic records), in regards to use of the ABPM device, and transmission of 24-hour BP readings to the Sponsor. A prior (b) (4) FDA inspection took place in the (b) (4) at a site in (b) (4) The focus of that inspection was on (b) (4) and the inspection was classified NAI.

During the inspection, the field investigators spot checked BP data from subjects at the following clinical investigator sites: Dr. Gigi Lefebrvre (Site 3019), Dr. Eli Roth (Site

3026), Dr. Meera Dewan (Site 3042) and Dr. Danilo Lopez (Site 2032) The inspection reviewed BP data for 9 subjects at Site 2032, 6 subjects at Site 3026, 8 subjects at Site 3042, and 9 subjects at Site 3019. The inspections at these clinical investigator sites were complete, and only minor regulatory violations were found at two sites (Dr. GiGi Lefebrvre and Dr. Danilo Lopez); the other two received NAI classifications.

The following are examples of documents collected and reviewed during the inspection:

- Master Agreement for Clinical Services;
- Scope of Work
- Task Order;
- Change Order
- Data Transfer Agreement for Study 302;
- ABPM Manual

With respect to Part 11 Regulations, to ensure proper use and design of the ABPM device, the field investigator reviewed the following:

- General validation for data transfer programming of Study 301;
- System security features (unique IDs, audit trails, encrypted passwords);
- Screen shots of SAS data export;
- Sample Quality Control (QC) Status Memo sent to sites for verification;
- Sample Database Lock Checklist

The observations noted were based on the EIR with supporting exhibits.

b**. General observations/commentary**:
During the inspection, the field investigators checked consistency between BP data in the Sponsor's data listings with BP measurements at the CRO site. The field investigators noted that the Sponsor provided BP readings as 24-hour "mean" values, whereas (b) (4) maintained the individual daily readings (taken every 15 minutes). To reconcile these methods, the field investigators did manual calculations (added up individual measurements) to corroborate the mean values provided from the Sponsor. These calculations did not reveal any discrepancies between average BP measurements by the Sponsor and the average BP measurements manually calculated.

As per (b) (4) considers themselves to be a Technical Service Provider, not a full-service CRO. Further, he explained the following operations that took place at (b) (4) with respect to receipt of BP data:

- After receiving data (electronically) from the clinical site, (b) (4) transmitted the data directly to Takeda;
- (b) (4) used CardioSpace and SAS to transfer the data to Takeda;
- (b) (4) used Microsoft Excel and CardioSpace to conduct quality control reviews and data queries;
- (b) (4) did not conduct any data analysis;
- After (b) (4) receives BP data from the site, an ABP Subject Summary report

was sent to the clinical site to document that a subject's BP data had either passed or failed study criteria.

In general, the inspection went well and no deficiencies were noted. The inspector looked at details on the design and use of the ABPM device used to collect BP readings as part of the NDA study. The inspection reviewed records related to the database design, audit trails, and other system security features, while using "print-screen-shots" as the primary documented exhibits. The ABPM device and computerized systems appeared to be designed and used correctly.

During their inspection, (b) (4) provided a tour of their Information Technology hardware on site used to store live servers and databases. The field investigators reported that the server room was secure with restricted access. No regulatory violations were identified during this inspection, and no Form FDA 483 was issued.

In general, the data management of the studies by (b) (4) appears adequate, QC processes were used to ensure proper functioning of the ABPM device, and the primary efficacy data were verified. The data generated appear acceptable in support of the respective indications for this NDA

c. **Assessment of data integrity**: In general, the data management of the studies by (b) (4) appears adequate, adequate Quality Control processes were used to ensure proper functioning of the ABPM device, and the primary efficacy data were verified. The data generated appear acceptable in support of the respective indications for this NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, inspection of the four clinical investigator sites (Lefebrvre, Roth, Dewan, Lopez) revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. Only minor regulatory violations were found at two sites (Dr. GiGi Lefebrvre and Dr. Danilo Lopez), and they received a VAI classification. The other two sites (Roth and Dewan) received NAI classifications.

The key regulatory violations at the Lopez site were failure to follow the investigational plan. Specifically, the inspection found that several lab tests (HbA1C and Chemistry Panel II), along with several pulse and weight measurements were missing for several subjects. The most notable observation was that Subject 047 was enrolled despite a screening EKG that revealed a silent myocardial infarction. However, a protocol violation report for this event was filed to the NDA. The noted regulatory violations are unlikely to significantly impact data reliability.

The key regulatory violation at the Lefebrvre site was also failure to follow the investigational plan. Specifically, there were several minor inconsistencies in manual BP readings between the worksheets and the e-CRF. The inspection also noted that manual BP readings were not re-taken for 6 subjects when successive diastolic BP differed by > 5 mm Hg. Given the sporadic nature of this violation, it appears that these protocol deviations would not significantly impact NDA analyses. The most notable observation at this site was the finding that BP readings were

not always taken at serum trough levels, as per the protocol which required BP readings be measured in the morning approximately 24 hours after the previous day's dose. For Subject 114, the review division may wish to consider if the timing of the BP assessments in Subject 114 would have a significant effect on the efficacy data reported for this subject. Although minor regulatory violations were noted, it is unlikely that these would significantly impact data reliability.

OSI conducted a CRO inspection of (b) (4) and included a Part 11 Clinical Inspectional assignment to ensure CRO and Sponsor understanding and compliance with 21 CRF 21 Part 11 regulations and guidance (electronic records), in regards to use of the ABPM device, and transmission of 24-hour BP readings to the Sponsor. No regulatory violations were noted during this inspection.

With the exception of the items noted above, the study appears to have been conducted adequately, and the data generated by these sites may be used in support of the respective indication.

NOTE: The observations at Dr. Dewan's site are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

{See appended electronic signature page}

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Date:	August 2, 2011
Application Type/Number:	NDA 202331
To:	Norman Stockbridge, MD, Director Division of Cardiovascular and Renal Products
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name and Strengths:	Edarbyclor (Azilsartan Medoxomil and Chlorthalidone) Tablets, (b) (4) 40 mg, 12/5 mg, 40 mg/25 mg, (b) (4)
Applicant/sponsor:	Takeda Pharmaceuticals
OSE RCM #:	2011-704

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1 INTRODUCTION

This review evaluates the container labels, carton, and prescribing information labeling of Edarbyclor (Azilsartan Medoxomil and Chlorthalidone) Tablets for the potential to contribute to medication errors. Additionally, this review evaluates the tablet appearance for the potential to contribute to medication errors per email request from the Division of Cardiovascular and Renal Products, dated March 24, 2011.

1.1 REGULATORY HISTORY

Edarbyclor Tablets indicated for the treatment of hypertension, is a subject of a 505 (b)(1) application, NDA 202331, submitted to the FDA on February 24, 2011. In the Investigational New Drug stage (IND 077278), the Applicant proposed to market (b) (4) (b) (4) (b) (4) 40 mg/12.5 mg, 40 mg/25 mg, (b) (4) and (b) (4) However, during the NDA stage the Applicant proposed to market (b) (4) (b) (4) 40 mg/12.5 mg, 40 mg/25 mg, and (b) (4) (b) (4)

The proposed proprietary name, Edarbyclor, was approved on July 12, 2011.

The single ingredient product, Edarbi that contains Azilsartan Medoxomil was approved in February 25, 2011.

1.2 PRODUCT INFORMATION

Edarbyclor (Azilsartan Medoxomil and Chlorthalidone) Tablets are indicated for the treatment of hypertension. The starting dose for this product is (b) (4) 40 mg/12.5 mg administered orally once daily. The dose may be increased after 2 weeks to 4 weeks as needed to control blood pressure. The maximally effective dose is 40 mg/25 mg. Currently, the Applicant proposes to market (b) (4) (b) (4) 40 mg/12.5 mg, 40 mg/25 mg, (b) (4). The product will be supplied in bottles containing 30 tablets and 90 tablets. Additionally, the product will be supplied in sample units. Each sample units contains 7 tablets. The proposed Azilsartan Medoxomil and Chlorthalidone Tablets should be dispensed and stored in original container to protect the product from light and moisture.

2 METHODS AND MATERIALS

Because the single ingredient Edarbi product is approved, we searched the FDA Adverse Event Reporting System (AERS) database to identify errors occurring with this product that may be indicative of errors that could occur with the new product.

Additionally, DMEPA evaluated the proposed container labels, carton, and prescribing information labeling for Azilsartan Medoxomil and Chlorthalidone using Failure Mode and Effects Analysis[1] (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

We also compared the proposed labels and labeling to those of Edarbi to ensure that these products are well-differentiated from each other to help minimize product selection errors.

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

2.1 FDA Adverse Event Reporting System Database (AERS) Selection of Cases

The AERS search conducted on July 6, 2011, used the following search terms: active ingredient "Azilsartan", trade name "Edarbi", and verbatim terms "Edar%" and "Azilsart%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and Product Quality Issues". No time limitations were set.

2.2 Labels, Labeling, and Packaging Risk Assessment

This review focused on the product's container labels, inner sleeve labels, carton, prescribing information labeling, and tablets' images submitted by the Applicant on June 23, 2011 (See Appendix A for the container labels, inner sleeve labels, carton labeling and Appendix B for images of tablets). [redacted] (b) (4) we evaluated appearance [redacted] (b) (4) for the potential to contribute to medication errors.

- Trade Container labels ([redacted] (b) (4) 40 mg/12.5 mg, 40 mg/25 mg, [redacted] (b) (4)): 30 tablets and 90 tablets
- Sample Inner Sleeve labels([redacted] (b) (4) 40 mg/12.5 mg, 40 mg/25 mg. [redacted] (b) (4) : 7 tablets
- Sample Carton labeling ([redacted] (b) (4) 40 mg/12.5 mg, 40 mg/25 mg, [redacted] (b) (4) one unit containing 7 tablets
- Sample Carton Labeling([redacted] (b) (4) 40 mg/12.5 mg, 40 mg/25 mg. [redacted] (b) (4) Five units, each containing 7 tablets
- Images of Edarbyclor Tablets: [redacted] (b) (4) [redacted] (b) (4) 40 mg/12.5 mg, 40 mg/25 mg, [redacted] (b) (4) .

We also evaluated the labels and labeling for Edarbi to ensure that the two products are well-differentiated (See Appendix B).

3 RESULTS

The following Sections describe the results of our searches and our evaluation of the labels and labeling.

3.1 FDA Adverse Event Reporting System (AERS) Database Results

Zero reports (n=0) were identified in the Adverse Event Reporting System (AERS) database.

3.2 Labels and Labeling Risk Assessment Results

Our evaluation of the container labels, inner sleeve, carton, and prescribing information labeling, as well as tablet appearance identified deficiencies that require revisions prior to approval to help minimize the risk of medication errors associated with the use of Edarbyclor:

- [redacted] (b) (4)
- The maximum daily dose of the product is 40 mg/25 mg. However, the Applicant proposes to [redacted] (b) (4)
- [redacted] (b) (4)
- The expression of strength throughout labels and labeling [redacted] (b) (4)

(b) (4)

- Container labels, inner sleeve labels, and carton labeling contains (b) (4)
- The imprint used on the tablets is appropriate. The shapes, sizes, and colors of lower strength tablets (b) (4)
- (b) (4)

4 DISCUSSION

(b) (4) Edarbyclor Tablets will be initiated at the dose of (b) (4) 40 mg/12.5 mg administered orally once daily. The maximum dose for this product is 40 mg/25 mg once daily. Thus, this strength is not appropriate because the maximum effective dose of the product is 40 mg/25 mg.

Other deficiencies noted with the labels and labeling include the lack of measurement units after the strength of each ingredient (b) (4) Units of measure should be placed after each ingredient (i.e., (b) (4) "40 mg/12.5 mg" "40 mg/25 mg", (b) (4)

The Applicant proposes to differentiate the tablets with appearance across the different strengths. By using imprinted markings of the strength on the tablet, the proposed product follows 21 CFR 206.10 (a) which states that:

...No drug product in solid dosage form may be introduced or delivered for introduction into interstate commerce unless it is clearly marked or imprinted with a code imprint that, in conjunction with the product's size, shape, and color permits the unique identification of the drug product and the manufacturer or distributor of the product...

Additionally, we find the use of imprinted markings of the strength on the tablet to be appropriate and helpful. However, the (b) (4) 40 mg/12.5 mg tablets, and 40 mg/25 mg tablets appear to have the same shape (circle) and similar sizes. Additionally, (b) (4) Thus, although Edarbyclor Tablets are in compliance with 21 CFR 206.10 (a), utilizing contrasting colors, sizes, and shapes to differentiate between the (b) (4) (b) (4) 40 mg/12.5 mg, and 40 mg/25 mg would be ideal. However, the labels and labeling will help to differentiate the proposed strengths.

5 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the container labels, inner sleeve, carton, and prescribing information labeling identified areas of improvements that will help minimize the risk of medication errors associated with the use of Edarbylcor. Thus, DMEPA recommends labeling revisions outlines below be implemented prior to approval of this product. Section 5.1 *Comments to the Division* contains our recommendations regarding prescribing information labeling. Section 5.2 *Comments to the Applicant* contains our recommendations regarding container labels, inner sleeve labels, and carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Phoung Nina Ton at 301-796-1648.

5.1 Comments to the Division

A. General Comments

1. [redacted] (b) (4) The maximum effective dose for this product is 40 mg/25 mg once daily. [redacted] (b) (4)

2. The tablets contain the clear imprint markings of the strength, which helps differentiate among different strengths of the product. However, the [redacted] (b) (4) [redacted] (b) (4) 40 mg/12.5 mg tablets, and 40 mg/25 mg tablets appear to have the same shape (circle) and similar sizes [redacted] (b) (4) These similarities do not help to differentiate the tablets effectively. Ideally, for maximum differentiation, different tablet shapes and colors would be helpful.

B. Prescribing Information Labeling

1. General Comments

   a. Revise the established name to state 'Azilsartan Medoxomil and Chlorthalidone'. As currently presented throughout prescribing information, the established name is presented as [redacted] (b) (4)

   b. Throughout the package insert, the strength presentation does not include a unit of measurement after the strength of each active ingredient (i.e., [redacted] (b) (4) "40/12.5 mg" "40/25 [redacted] (b) (4) Thus, revise the presentation of the strengths as follows:

      [redacted] (b) (4) "40 mg/12.5 mg" "40 mg/25 mg", [redacted] (b) (4)".

2. *Dosage and Administration*, Highlights of Prescribing information

   To improve sentence clarity, revise the phrase "2-4 weeks" to read "2 weeks to 4 weeks".

3. Section 2.1, *General Considerations*

   To improve sentence clarity, revise the phrase "1-2 weeks" to read "1 week to 2 weeks" and "2-4 weeks" to read "2 weeks to 4 weeks".

4. Section [redacted] (b) (4)

   [redacted] (b) (4) "Dispense and store Edarbyclor in its original container to protect Edarbyclor from light and moisture. [redacted] (b) (4)

5. Section 3, *Dosage Forms and Strength*

   Revise the first sentence "Edarbyclor is supplied in the following dosage strengths:" to state "Edarbyclor (Azilsartan Medoxomil and Chlorthalidone) Tablets is supplied in the following dosage strengths:".

6. Section 16, *How supplied*

a. Remove the space between the strengths of Azilsartan Medoxomil and Chlorthalidone and place the measuring units for Azilsartan Medoxomil in milligrams (i.e., [redacted] (b) (4) 40 mg/12.5 mg, [redacted] (b) (4) and 40 mg/25 mg).

b. Revise the headings [redacted] (b) (4) to read "Bottle of 30 tablets" and "Bottle of 90 tablets". As currently presented these headings are confusing and may be misinterpreted.

c. Write out the entire NDC number. As currently presented, the NDC numbers are confusing.

d. We recommend adding a sentence stating that Edarbyclor tablets are not scored. DMEPA has post-marketing cases involving other non-scored oral tablets that were broken, chewed, or divided. As a result, patients received over- and under-doses of the product. Thus, the statement that the tablets are not scored may help to minimize this type of error.

e. Revise the heading [redacted] (b) (4) to state the word 'Strength of Edarbyclor' to clarify that the numbers refer to the strengths of the product. Thus, the table should be revised as follows:

Strength of Edarbyclor Tablets	NDC Numbers	
	Bottle of 30 tablets	Bottle of 90 tablets
[redacted] (b) (4)		
40 mg/12.5 mg	64764-944-30	64764-944-90
[redacted] (b) (4)		
40 mg/25 mg	64764-994-30	64764-994-90

5.2 Comments to the Applicant

A. All Container Labels, Sample Inner Sleeve Labels, and Sample Carton Labeling

([redacted] (b) (4) 40 mg/12/5 mg, 40 mg/25 mg, [redacted] (b) (4))

1. [redacted] (b) (4) Additionally, consider using a different layout, font type, and font style for all labels and labeling of Edarbyclor to further differentiate from the labels and labeling of Edarbi.

2. [redacted] (b) (4)

(b) (4) the most important information on the labels and labeling such as proprietary and established names, dosage form, and strength.

3. The established name, dosage form and strength should be presented as follows (Example):

   Azilsartan Medoxomil and Chlorthalidone Tablets
   (b) (4)

   Additionally, increase the prominence of the strength by increasing the font size of this statement.

4. (b) (4)

5. (b) (4)

6. (b) (4)

B. Container Label ((b) (4) 40 mg/12/5 mg, 40 mg/25 mg, (b) (4))

Increase the prominence of the net quantity by increasing the font size. As currently represented, it can be easily overlooked. However, ensure it is not as prominent as the most important information on the principle display panel such as established name and strength.

C. Sample Carton Labeling ((b) (4) 1 x 40 mg/12/5 mg, 1 x 40 mg/25 mg, (b) (4))

1. Increase the prominence of a diagram showing how to extract the inner sleeve packaging from the carton to increase readability and clarity of the diagram. As currently presented, the diagram is very small and is hard to read.
2. Although the Usual Dosage statement is in compliance with the 21 CFR 201.55, it is important to include the exact dosing information on the principle display panel because the sample units may be dispensed without additional labels directly to the patient. Thus, we recommend revising the Usual Dosage statement to read "Usual Dosage: one tablet daily".
3. Add the phrase "per tablet" after the strength.
4. Increase the prominence of the statement "Protect from moisture and light. Dispense and store in original container" by using bold font.
5. Decrease prominence of the statement "Professional Sample-Not for Sale" by unbolding it.
6. Revise the statement (b) (4) to increase the clarity of the statement. The revised statement should read "One patient sample unit contains 7 tablets".

D. Sample Carton Labeling ((b) (4) 5 x 40 mg/12/5 mg, 5 x 40 mg/25 mg, (b) (4))

1. Although the Usual Dosage statement is in compliance with the 21 CFR 201.55, it is important to include the exact dosing information on the principle display panel because the sample units may be dispensed without additional labels directly to the patient. Thus, we recommend revising the Usual Dosage statement to read "Usual Dosage: one tablet daily".
2. Add the phrase "per tablet" after the strength.
3. Increase the prominence of the statement "Protect from moisture and light. Dispense and store in original container" by using bold font.
4. Decrease prominence of the statement "Professional Sample-Not for Sale" by unbolding it.

E. Inner Sleeve Label ((b) (4) 1 x 40 mg/12/5 mg, 1 x 40 mg/25 mg, (b) (4))

1. Add the phrase "per tablet" after the strength.
2. Add the net quantity statement to the principle display panel that will state (b) (4) Ensure the net quantity statement does not compete for prominence with the most important information on the principle display panel such as established name and strength.
3. Revise the statement (b) (4) to read "Usual Dosage: one tablet daily". Since the sample units may be dispensed without additional labels directly to the patient, it is important to have the dosing instructions on the principle display panel.
4. Add the statement regarding tablet contents (i.e., each tablet contains…) to the back panel of the label.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

YELENA L MASLOV
08/02/2011

YELENA L MASLOV on behalf of ZACHARY A OLESZCZUK
08/02/2011

CAROL A HOLQUIST
08/03/2011

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 202-331

Name of Drug: Edarbyclor (azilsartan medoxomil plus chlorthalidone) Tablets

Applicant: Takeda Pharmaceuticals North America

Labeling Reviewed

Submission Date: February 24, 2011

Receipt Date: February 24, 2011

Background and Summary Description

Takeda Pharmaceuticals has submitted this 505(b)(2) NDA for Edarbyclor, an oral, fixed-dose combination (FDC) tablet containing TAK-491 (azilsartan medoxomil) and chlorthalidone. TAK-491 is a pro-drug that is rapidly hydrolyzed to TAK-536 (azilsartan), an antagonist of the angiotensin II type I receptor. Chlorthalidone is a thiazide-like diuretic that has been marketed in the US since 1959. The monotherapy NDA for azilsartan medoxomil was approved on February 25, 2011 for the treatment of hypertension under the tradename Edarbi (NDA 200-796). For the fixed dose combination, Edarbyclor, the proposed indication is the treatment of hypertension, including initial therapy. (b) (4) dosage strengths of Edarbyclor are being proposed: (b) (4) 40/12.5, (b) (4) and 40/25 mg.

An EOP1 meeting was held on 4-4-06. Pre-NDA meetings were cancelled because the Pre-NDA Meeting Preliminary Responses for the non-clinical and CMC sections (dated 9-9-10) and clinical and clinical pharmacology sections (dated 11-8-10) were sufficient.

This NDA is an electronic submission which follows the eCTD guidance. Draft labeling was submitted for the Package Insert (PI), Patient Package Insert (PPI), and Carton and Container. The PI was submitted in PLR format. Electronic Content of Labeling was submitted in SPL format.

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an "X."

Reference ID: 2941336

Recommendations

All labeling issues identified on the following pages with an "X" will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues. The resubmitted labeling will be used for further labeling discussions.

Quynh Nguyen, PharmD, RAC	5-3-11
Regulatory Project Manager	Date

Reference ID: 2941336

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state “None”)
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

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- **Highlights Limitation Statement**

  ☒ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

- **Product Title**

  ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

  ☒ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

  ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."

  ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.

  ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

  ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

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- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☒ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☒ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**.

- **Revision Date**

  ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

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Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☒ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

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- **Adverse Reactions**

  ☒ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

  ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

  > "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

  ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

  > "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**

  ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

  ☐ This section is required and cannot be omitted.

  ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

  - "See FDA-approved patient labeling (Medication Guide)"
  - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
  - "See FDA-approved patient labeling (Patient Information)"
  - "See FDA-approved patient labeling (Instructions for Use)"
  - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Reference ID: 2941336

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QUYNH M NGUYEN
05/03/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202331 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Edarbyclor Established/Proper Name: azilsartan medoxomil plus chlorthalidone Dosage Form: Tablets Strengths: (b) (4) 40/12.5, (b) (4) 40/25 mg		
Applicant: Takeda Pharmaceuticals North America Agent for Applicant (if applicable):		
Date of Application: 2-24-11 Date of Receipt: 2-24-11 Date clock started after UN:		
PDUFA Goal Date: 12-24-11	Action Goal Date (if different): 12-23-11	
Filing Date: 4-25-11	Date of Filing Meeting: 4-4-11	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): Treatment of hypertension, including initial therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

Reference ID: 2941331

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 77,278 and 71,867	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

Reference ID: 2941331

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm **If yes**, please list below:	X			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
N200796	Edarbi (azilsartan medoxomil) Tablet	NCE	February 25, 2016

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Reference ID: 2941331

Designations and Approvals list at: ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***				

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If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Reference ID: 2941331

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

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Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	This is an electronic submission.

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Full waiver request included.

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

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If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		EOP1 meeting on 4-6-06

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Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 9-9-10 (Non-clin and CMC); 11-8-10 (Clin and clin pharm) ***If yes, distribute minutes before filing meeting***	X			Meetings were cancelled because Prelim Responses were sufficient.
Any Special Protocol Assessments (SPAs)? **Date(s):** 11-24-09 (Agreement); 9-10-09 (No agreement) ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

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ATTACHMENT

MEMO OF FILING MEETING

DATE: 4-4-11

BLA/NDA/Supp #: NDA 202-331

PROPRIETARY NAME: Edarbyclor

ESTABLISHED/PROPER NAME: azilsartan medoxomil plus chlorthalidone

DOSAGE FORM/STRENGTH: Tablets, (b) (4) 40/12.5, (b) (4) 40/25 mg

APPLICANT: Takeda Pharmaceuticals North America

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of hypertension, including initial therapy.

BACKGROUND: Edarbyclor is an oral, fixed-dose combination tablet containing TAK-491 (azilsartan medoxomil) and chlorthalidone. TAK-491 is a pro-drug that is rapidly hydrolyzed to TAK-536 (azilsartan), an antagonist of the angiotensin II type I receptor. Chlorthalidone is a thiazide-like diuretic that has been marketed in the US since 1959. The monotherapy NDA for azilsartan medoxomil was approved on February 25, 2011 for the treatment of hypertension under the tradename Edarbi (NDA 200796). The proposed indication for the fixed dose combination of TAK-491 and chlorthalidone is for the treatment of hypertension, including initial therapy. (b) (4) dosage strengths of TAK-491CLD are being proposed: (b) (4) 40/12.5, (b) (4) and 40/25 mg.

In support of approval, the sponsor has submitted efficacy and safety results from seven Phase 3 studies, in which 2358 subjects received TAK-491CLD and 819 subjects received TAK-491 coadministered with chlorthalidone. Of these, 4 studies were conducted with the FDC tablet (studies 302, 306, 301, and 308). The pivotal study, 491CLD-302, was an 8-week, randomized, double-blind, controlled, fixed-dose, factorial study that evaluated the efficacy and safety of TAK-491CLD relative to TAK-491 and chlorthalidone monotherapies. The other three FDC studies were designed to compare TAK-491CLD with active comparators. Additionally, supportive data from three coadministration studies (i.e.,TAK-491 plus chlorthalidone) were resubmitted from the TAK-491 monotherapy program; these studies include a short-term, double-blind, randomized, placebo-controlled study and two long-term, open-label safety studies.

An EOP1 meeting was held on 4-4-06. Pre-NDA meetings were cancelled because the Pre-NDA Meeting Preliminary Responses for the non-clinical and CMC sections (dated 9-9-10) and clinical and clinical pharmacology sections (dated 11-8-10) were sufficient.

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REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Quynh Nguyen	Y
	CPMS/TL:	Ed Fromm	Y
Cross-Discipline Team Leader (CDTL)	Shari Targum		Y
Clinical	Reviewer:	Khin U	Y
	TL:	Tom Marciniak	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Divya Menon-Andersen	Y
	TL:	Raj Madabushi	N
Biostatistics	Reviewer:	Jialu Zhang	Y
	TL:	Jim Hung	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Philip Gatti	Y
	TL:	Al DeFelice	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Prafull Shiromani	N

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	TL:	Kasturi Srinivasachar	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	DCRP: Tim Link OSE: Eileen Wu, Nina Ton		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

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If no, explain:	
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: This is an NDA for a combination product of two approved drugs and is not an NME. ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE

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Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Norman Stockbridge, MD, PhD **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

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	• notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

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Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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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.

/s/

QUYNH M NGUYEN
05/03/2011