

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202331Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.5.2 PATENT CERTIFICATION

Paragraph I and II Certification

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and the Food and Drug Administration regulations and codified in 21 USC §355(b)(2)(A) and 21 CFR §314.50(i)(1)(i)(A), Takeda Global Research & Development Center, Inc. (TGRD) hereby certifies to the best of our knowledge that patent information has not been filed with the Agency for chlorthalidone, the reference drug component of the TAK-491CLD drug product in this application. We understand that information regarding one patent, U.S. Patent No. 4,933,360, was listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) with NDA No. 19-574 for THALITONE (chlorthalidone) tablets, however that patent expired on June 12, 2007, and has not been listed since that time. Information provided in the Orange Book (updated April 29, 2011) indicate there are no unexpired patents or unexpired exclusivities claimed for the reference drug chlorthalidone.

Please see attached approval page for electronic approval of this document.

Beth-Anne Knapp, MBA, RAC
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development

Date

CONFIDENTIAL

EXCLUSIVITY SUMMARY

NDA # 202-331

SUPPL #

HFD # 110

Trade Name Edarbyclor Tablets

Generic Name azilsartan medoxomil and chlorthalidone

Applicant Name Takeda Pharmaceuticals North America

Approval Date, If Known December 20, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 200-796 Edarbi (azilsartan medoxomil) Tablets

NDA# 12-283 Hygroton (chlorthalidone) Tablets

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 302 (pivotal) and Studies 306, 301, 303, and 308 (supportive)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Study 302 (pivotal) and Studies 306, 301, 303, and 308 (supportive)

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 302 (pivotal) and Studies 306, 301, 303, and 308 (supportive)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 77,278 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES
Explain: ! NO
! Explain:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Quynh Nguyen, PharmD, RAC
Title: Regulatory Project Manager, Division of Cardiovascular and Renal Products
Date: 12-20-11

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Division Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

NORMAN L STOCKBRIDGE
12/20/2011

This certification is provided for New Drug Application (NDA 202,331, azilsartan medoxomil and chlorthalidone fixed-dose combination). Takeda Global Research & Development Center, Inc. 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.

Please see attached approval page for electronic approval of this document.

Jenipher Dalton
Director, Clinical Quality Assurance
Takeda Global Research and Development Center, Inc.

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202331 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Edarbyclor Established/Proper Name: azilsartan medoxomil and chlorthalidone Dosage Form: Tablet		Applicant: Takeda Pharmaceuticals North America Agent for Applicant (if applicable):
RPM: Quynh Nguyen, PharmD, RAC		Division: DCRP
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>NDA 200796 Edarbi (azilsartan medoxomil) Tablet NDA 12-283 Hygroton (chlorthalidone) Tablet</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This product is a fixed dose combination of azilsartan medoxomil and chlorthalidone.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 24, 2011</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 4</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	12-20-11
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 12-20-11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	12-16-11
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	12-16-11
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	11-29-11
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Non-acceptable Review and Letter dated 2-25-11; Minutes of 4-6-11 Type C Mtg; Proprietary Name Request WD Letter dated 4-28-11; Acceptable review and Letter dated 7-12-11 Final review dated 12-5-11
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 5-3-11 <input checked="" type="checkbox"/> DMEPA 2-25-11; 8-2-11; 12-9-11 <input checked="" type="checkbox"/> DRISK 11-7-11 <input checked="" type="checkbox"/> DDMAC 11-10-11 <input checked="" type="checkbox"/> SEALD 12-16-11 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM Filing Review (5-3-11); Medical filing review (3-11-11); Statistical filing review (4-4-11); Clinical Pharm filing review (4-4-11); Initial Quality Assessment (3-18-11) <input type="checkbox"/> Not a (b)(2) 12-15-11 <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>7-13-11</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg 9-9-10 (Non-clin and CMC Prelim Responses); 11-8-10 (Clin and clin pharm Prelim Responses)
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	EOP1 mtg on 4-6-06; Pre-IND mtg on 11-14-07
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12-16-11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11-10-11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None (1) 11-22-11
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	NA
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	10-3-11; 3-11-11
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See 10-3-11 Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 10-18-11
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8-6-11; 11-28-11; 12-15-11
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-4-11
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7-18-11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None Product quality: 7-11-11; 11-1-11 Biopharm: 10-24-11
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		7-11-11
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>		Date completed: 5-20-11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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/s/

QUYNH M NGUYEN
12/21/2011

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266**

Transmitted via email to: beth.knapp@takeda.com

Attention: Beth-Anne Knapp, MBA, RAC

Sponsor: Takeda Global Research & Development Center, Inc.

Phone: (224) 554-2187

Subject: **Type C Guidance Teleconference Minutes**

Date: December 19, 2011

Pages including this sheet: 26

From: Quynh Nguyen, Pharm.D., RAC
Phone: 301-796-0510
Fax: 301-796-9838
E-mail: quynh.nguyen@fda.hhs.gov

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Type C Guidance Meeting via Teleconference with Sponsor

Application Number: NDA 202-331
Sponsor: Takeda Global Research & Development Center, Inc.
Drug: Edaryclor (TAK-491/chlorthalidone)
Type of Meeting: Guidance
Classification: C
Meeting Date: December 12, 2011
Confirmation Date: December 9, 2011
Meeting Request Received: December 9, 2011
Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Recorder: Quynh Nguyen, Pharm.D., RAC

List of Attendees:

Food and Drug Administration

Office of New Drugs, Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.

Director

Khin Maung U, M.D.

Clinical Reviewer

Quynh Nguyen, Pharm.D., RAC

Regulatory Health Project Manager

Takeda Global Research & Development Center, Inc.

Stuart Kupfer, M.D.

Vice President, Clinical Sciences

Alison Handley, Ph.D.

Director, Clinical Sciences

Beth-Anne Knapp, M.B.A., RAC

Associate Director, Regulatory Strategy

Binita Kwankin

Senior Director, Regulatory Strategy

Una Ortell Director

Promotional Regulatory

BACKGROUND

Edarbyclor (TAK-491/chlorthalidone (CLD)) is a fixed-dose combination product of TAK-491, an angiotensin II receptor blocker, plus CLD, a thiazide-type diuretic. Takeda submitted an NDA for Edarbyclor on February 24, 2011 for the treatment of hypertension, including initial therapy. The Division's comments on the proposed labeling were sent to the sponsor on November 25, 2011 and on December 1 and 9, 2011. Upon receipt of the Division's December 9, 2011 labeling revisions, the sponsor requested a teleconference to understand the Division's rationale for deleting the following proposed paragraph from section 14 CLINICAL STUDIES, (b) (4)

(b) (4)

DISCUSSION DURING MEETING

Dr. Stockbridge began the teleconference by acknowledging that language specific for the combination products was not addressed in the Guidance for Industry, *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims*, as it should have been.

He noted, however, that there are different approaches for the labeling of combination products. For example, there are differences in labeling combination products used to treat a single disease, such as Edarbyclor, versus those used in a setting to treat multiple conditions solely for convenience, such as the pravastatin and aspirin combination. In the case of pravastatin and aspirin, the trial data for each monotherapy component is included in the labeling of the combination. However, with a single indication, such as for the combination anti-hypertensive products, the clinical trials section of the labeling only includes a description of the combination factorial trial data, and not the trial data for each of the components which received the original antihypertensive claim. Therefore, following this example, the Division deleted the paragraph referencing (b) (4) from the Edarbyclor labeling under section **14 CLINICAL STUDIES**.

Dr. Stockbridge also noted concern that the clinical studies section of the labeling of a combination product could become ponderous if information is included for the double and triple combination products to the extent that the descriptions dominate the section. An example of such a draft label for another combination product was recently reviewed by the Division. Dr. Stockbridge acknowledged that the sponsor's paragraph regarding (b) (4) proposed only a few lines of text, but if the Division were to approve this paragraph, then it would have to be allowed for all other product labels also.

Dr. Stockbridge emphasized, however, that the Division would like to promote the principles of the Guidance with Edarbyclor and he hoped that the sponsor's advertising materials would make use of the statements under section **1 INDICATIONS AND USAGE** regarding the benefits of lowering blood pressure. Dr. Stockbridge thought that the statements under section **14 CLINICAL STUDIES** would support reference to (b) (4) in the sponsor's promotional materials (b) (4)

He added that as this approach would be consistent with the Guidance, the Division would be willing to support this promotional strategy and work with the Office of Prescription Drug Promotion, if needed. The sponsor commented that they were planning to present an evidence-based approach in line with the Guidance to promote Edarbyclor.

The sponsor asked whether they could include (b) (4) information as a reference to the Full Prescribing Information, e.g. as a footnote. Dr. Stockbridge replied that for the reasons cited before, the Division could not allow references to be included. However, the Division would be amenable to this proposal if it were needed to allay OPDP's concerns.

Dr. Stockbridge encouraged the sponsor to obtain feedback on their promotional materials from both the Division and OPDP in parallel since the promotion of the cardiovascular outcomes in the labeling also represents a more recent topic.

CONCLUSION

This meeting was scheduled to discuss the Division's rationale for deleting the paragraph regarding specific (b) (4) in section **14 CLINICAL STUDIES** of the sponsor's proposed labeling.

Minutes preparation: Quynh Nguyen, Pharm.D., RAC

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

NDA 202-331
Edarbyclor
Takeda
Page 4 of 26

Rd:
N Stockbridge 12/16/11
K U 12/16/11

Attachment: Proposed PI with Division changes dated 12-9-11

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/s/

NORMAN L STOCKBRIDGE
12/19/2011



NDA 202331

LABELING PMR/PMC DISCUSSION COMMENTS

Takeda Pharmaceuticals North America
Attention: Ms. Beth-Anne Knapp, MBA, RAC
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

Please refer to your New Drug Application (NDA) dated February 24, 2011, received February 24, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Edarbyclor (azilsartan medoxomil plus chlorthalidone) Tablets, (b) (4) 40/12.5, (b) (4) 40/25 mg.

We also refer to our May 4, 2011 Filing Communication, letter in which we notified you of our target date of November 25, 2011 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.”

On June 23, 2011, we received your June 23, 2011 updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

If you have any questions, please contact me at (301) 796-0510.

Sincerely,

{See appended electronic signature page}

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: DRAFT revised PI and Patient PI

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/s/

QUYNH M NGUYEN
11/25/2011

Nguyen, Quynh M

From Knapp, Beth Anne (TGRD) [beth.knapp@takeda.com]
Sent Monday, November 07, 2011 5:59 PM
To Knapp, Beth Anne (TGRD); Henry, Don
Cc Nguyen, Quynh M; Stanek, Jennifer (TGRD)
Subject RE: Post-marketing commitment for TAK-491CLD

Dear Don –

I want to just add some additional clarification to this commitment.

Yes, Takeda commits to submit a report that includes the justification to support the re-evaluation of the dissolution acceptance criteria for all strengths of both azilsartan medoxomil and chlorthalidone on or before December 24, 2012. Please note that the justification to support this re-evaluation will include all dissolution data generated to date (i.e. 12/24/12) including registration, PQ and post-approval commercial lots (both release and stability) as this will provide a larger body of data from which meaningful specifications can be derived.

Please let me know if you have any questions.

All the best,
 Beth

Beth-Anne Knapp, MBA, RAC
 Associate Director, Cardiovascular
 Regulatory Affairs Strategy
 Takeda Global Research & Development Center, Inc.
 One Takeda Parkway, Deerfield, IL 60015
 Office: 224.554.2187
 (b) (6) beth.knapp@takeda.com

From: Knapp, Beth Anne (TGRD)
Sent: Monday, November 07, 2011 12:51 PM
To: 'Henry, Don'
Cc: Nguyen, Quynh M; Stanek, Jennifer (TGRD)
Subject: RE: Post-marketing commitment for TAK-491CLD

Dear Don –

I hope this email finds you well. Thank you so kindly for your follow-up on this post marketing commitment.

Yes, Takeda commits to submit a report that includes the justification to support the re-evaluation of the dissolution acceptance criteria for all strengths of both azilsartan medoxomil and chlorthalidone on or before December 24, 2012.

In addition, please note that all post action communication related to CMC (quality) for both NDA 202-331 (Edarbyclor) and NDA 200-796 (Edarbi) can be directed to Jennifer Stanek. Here are her contact details for your records:

Jennifer Stanek, Associate Director
 Regulatory Affairs – CMC
 One Takeda Parkway
 Deerfield, IL 60015
 Phone: 224.554.3002
 Email: Jennifer.Stanek@takeda.com

Thank you again!

Quynh – I am the point of contact for all other correspondence besides CMC (quality).

All the best,
 Beth

Beth-Anne Knapp, MBA, RAC
 Associate Director, Cardiovascular
 Regulatory Affairs Strategy
 Takeda Global Research & Development Center, Inc.
 One Takeda Parkway, Deerfield, IL 60015
 Office: 224.554.2187
 (b) (6) beth.knapp@takeda.com

From: Henry, Don [mailto:Don.Henry@fda.hhs.gov]
Sent: Monday, November 07, 2011 10:03 AM
To: Knapp, Beth Anne (TGRD)
Cc: Nguyen, Quynh M
Subject: Post-marketing commitment for TAK-491CLD

Hello Beth

As discussed in our teleconference, Takeda will evaluate the dissolution data gathered 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 report that includes the justification to support the re-evaluation of the dissolution acceptance criteria for all strengths of both azilsartan medoxomil and chlorthalidone.

Based on the meeting this report will be submitted on or before Dec 24, 2012.

Does Takeda agree to this post-marketing commitment?

Thanks
 Don

Don L. Henry
 Food and Drug Administration

CDER/Office of New Drug Quality Assessment
Phone: 301-796-4227
Don.Henry@fda.hhs.gov

###

The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and is the property of Takeda. U

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/s/

QUYNH M NGUYEN
11/16/2011



NDA 202331

INFORMATION REQUEST

Takeda Pharmaceuticals North America
Attention: Ms. Beth-Anne Knapp, MBA, RAC
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

Please refer to your New Drug Application (NDA) dated February 24, 2011, received February 24, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Edarbyclor (azilsartan medoxomil plus chlorthalidone) Tablets, (b) (4) 40/12.5, (b) (4) 40/25 mg.

We also refer to your submission dated October 27, 2011 containing your response to our Information Request letter dated October 20, 2011 regarding the draft carton and container labeling.

We have reviewed your response and we have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We find that all of the carton and container labels with the exception of Edarbyclor 40 mg/25 mg are acceptable. However, (b) (4) utilized to highlight the strength of Edarbyclor 40 mg/25 mg is very similar to (b) (4) of the currently marketed product, Edarbi 40 mg, which provides additional similarity between the two products. Edarbi and Edarbyclor have similar names, so they will likely be close to one another when they are sitting on a shelf. Additionally, both products have partial overlap in strength (40 mg of azilsartan medoxomil). Thus, the use of (b) (4) may increase the potential for selecting the wrong product between Edarbi and Edarbyclor. Please revise (b) (4) used to highlight the strength of Edarbyclor 40 mg/25 mg, so that it does NOT overlap with Edarbi 40 mg or 80 mg (b) (4). We realize there is a limited number of colors from which to choose; however, we suggest yellow or brown/tan as these colors have not been used within either of your product lines.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
11/03/2011



NDA 202331

INFORMATION REQUEST

Takeda Pharmaceuticals North America
Attention: Ms. Beth-Anne Knapp, MBA, RAC
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

Please refer to your New Drug Application (NDA) dated February 24, 2011, received February 24, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Edarbyclor (azilsartan medoxomil plus chlorthalidone) Tablets, (b) (4) 40/12.5, (b) (4) 40/25 mg.

We also refer to your submission dated October 7, 2011 containing your response to our Information Request letter dated September 23, 2011 regarding the draft carton and container labeling.

We have reviewed your response and we have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A. All Container Labels, Sample Labels and Carton Labeling

1. All strengths of Edarbyclor have a (b) (4) (b) (4) can lead to selection errors among different Edarbyclor strengths. Thus, delete (b) (4)
2. (b) (4) utilized to highlight the strength of Edarbyclor 40 mg/25 mg is the same as (b) (4) of the currently marketed product, Edarbi 40 mg, (b) (4) Because these products will be located near one another on pharmacy shelves, the use of (b) (4) may increase the potential for selection errors between Edarbi and Edarbyclor. Thus, revise (b) (4)
3. The use of the negative prominent statement (b) (4) Thus, delete this statement.
4. Increase the prominence of the statement "Dispense and store in original container" by increasing the font size, bolding, and relocating it to the left corner of the principle display panel where the statement (b) (4) was previously located.

B. Front of the Sample Label

1. Add the proprietary name, established name, dosage form, and strength to the label. Currently, the label lacks this information, which is confusing.
2. Add the statement "per tablet" next to the strength of the product.
3. Delete the (b) (4) The product should be administered once daily without any cyclical pattern. (b) (4)

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
10/20/2011



NDA 202331

INFORMATION REQUEST

Takeda Pharmaceuticals North America
Attention: Ms. Beth-Anne Knapp, MBA, RAC
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

Please refer to your New Drug Application (NDA) dated February 24, 2011, received February 24, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Edarbyclor (azilsartan medoxomil plus chlorthalidone) Tablets, (b) (4) 40/12.5, (b) (4) 40/25 mg.

We also refer to your submission dated June 23, 2011 containing the 120-Day Safety Update, which included your updated proposed carton and container labeling.

We have reviewed your proposed carton and container labeling and we have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

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

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

1. (b) (4)

Additionally, all the labels and labeling of the proposed product use similar layout, font type, and font style to present the information as the currently marketed Edarbi, which may also lead to selection errors. (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. Delete (b) (4) intervenes with the readability of the proprietary name. Additionally, (b) (4) competes with 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.

Add an asterisk before the word “Each” in the phrase “Each tablet contains:” so that it is presented as follows:

*Each tablet contains:

(b) (4) azilsartan kamedoxomil (equivalent to (b) (4) azilsartan medoxomil) and 12.5 mg chlorthalidone

4. Delete (b) (4)

Once the established name, dosage form, and strength are revised, this statement will be unnecessary and redundant.

5. Delete (b) (4)

This information already appears with the established name and strength and is redundant and unnecessary.

6. Reverse the order of the two sentences: (b) (4) “Dispense and store in original container”. The use of the negative statement first, may be misinterpreted as (b) (4). The sentence order should be revised as follows: “Dispense and store in original container. (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 principal 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 principal 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 principal 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 “Contains one patient sample unit of 7 tablets each”. Ensure the net quantity statement does not compete for prominence with the most important information on the principal 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 principal display panel.
4. Add the statement regarding tablet contents (i.e., each tablet contains...) to the back panel of the label.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
09/23/2011



NDA 202331

INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Beth-Anne Knapp, MBA, RAC
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAK-491CLD (azilsartan medoxomil/chlorthalidone) Tablet.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Your proposed dissolution method as shown below is found acceptable.

Apparatus: USP II (paddle) with 50 rpm
Medium: 900 ml of pH 6.8 phosphate buffer containing 1.0% Tween 80, at 37°C
Sampling time: 10, 15, 20, 30, and 45 min

However, the proposed dissolution specifications need to be tightened for both azilsartan medoxomil and chlorthalidone as shown below and the Agency's proposed specifications should be implemented accordingly. Provide an updated drug product specification for all strengths.

Specifications:

From: Q= (b) (4) at 30 min for both azilsartan medoxomil and chlorthalidone

To: Q= (b) (4) at 30 min for azilsartan medoxomil and
Q= (b) (4) at 15 min for chlorthalidone

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
08/08/2011



NDA 202331

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Takeda Pharmaceuticals North America
One Takeda Parkway
Deerfield, IL 60015

ATTENTION: Beth-Anne Knapp, MBA, RAC
Associate Director, Regulatory Affairs

Dear Ms. Knapp:

Please refer to your New Drug Application (NDA) dated February 21, 2011, received February 24, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azilsartan Medoxomil and Chlorthalidone Tablets, (b) (4) 40 mg/12.5 mg, (b) (4) and 40 mg/25 mg.

We also refer to your April 13, 2011, correspondence, received April 13, 2011, requesting review of your proposed proprietary name, Edarbyclor. We have completed our review of the proposed proprietary name, Edarbyclor and have concluded that it is acceptable.

The proposed proprietary name, Edarbyclor, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 13, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Quynh Nguyen at 301-796-0510.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/12/2011



NDA 202331

INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Beth-Anne Knapp, MBA, RAC
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAK-491CLD (azilsartan medoxomil/chlorthalidone) Tablet.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. DMF # (b)(4) for Chlorthalidone drug substance

This DMF was determined to be inadequate on review to support this NDA and hence, a deficiency letter has been sent to the DMF holder.

2. P.2.3 Manufacturing Process Development –Tablet Content Uniformity

You propose a control strategy, (b)(4)

(b)(4) however, you did not provide any explanation of this control strategy adopted on commercial scale; accordingly, provide details of this strategy.

3. P.2.3 Manufacturing Process Development - Dissolution of CLD at (b)(4) minutes

- a. In the 'Actual by Predicted Plot' (Figure 22) the Rsq value of (b)(4) is low and the RMSE value of (b)(4) is high indicating that the model is inadequate to describe the data; provide explanation for this inadequacy.
- b. During your comprehensive study of factors affecting tablet dissolution, have you studied the combined effect (b)(4) on tablet dissolution. If so, provide details. Your 'Prediction Profiler' plots show opposite effects of these independent variables on CLD dissolution (b)(4) minutes, as expected.

4. P.5.1 Specification(s)

a.

[Redacted] (b) (4)

- b. To comply with USP <467> include a test for the control of residual solvents in the drug product [Redacted] (b) (4)
- c. The USP monograph for chlorthalidone tablets has assay limits of 92-108%; accordingly, these limits should be reflected in your drug product specification.
- d. Provide a revised drug product specification with the above item/s reflected there-in.

5. P.5.2 Analytical Procedures

- a. Since your drug product is a combination product, clarify with explanation which drug substance peak in the chromatogram for related substances is used to calculate the amount of an unspecified impurity?
- b. You have provided two alternative procedures, a primary method and an alternative method, in the product specification for assay, content uniformity, related substances and dissolution; however, no study is presented to demonstrate equivalency and hence, interchangeability between these methods. Provide data to show that the primary and alternative methods are equivalent and hence, interchangeable.

6. P.8.1 Stability

Since you are requesting a 30-month expiration dating period for the product in the bottles, include a 30-month test time period in the stability protocol for the bottles.

7. R1 Executed Batch Records

Clarify the discrepancy between

[Redacted] (b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
06/27/2011



NDA 202331

FILING COMMUNICATION

Takeda Pharmaceuticals North America
Attention: Ms. Beth-Anne Knapp, MBA, RAC
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

Please refer to your New Drug Application (NDA) dated February 24, 2011, received February 24, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Edarbyclor (azilsartan medoxomil plus chlorthalidone) Tablets, (b) (4) 40/12.5, (b) (4) 40/25 mg.

We also refer to your submissions dated March 3 and 9, and April 1, 6, 7, 8, 13, 19 and 22, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 24, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 25, 2011.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Under the HIGHLIGHTS OF PRESCRIBING INFORMATION,
 - a. Change the text "HIGHLIGHTS" to lowercase in the Highlights limitation statement so that it reads 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).**"
 - b. Insert a line space between the Highlights limitation statement and the product title.
 - c. The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new combination of active ingredients must be placed immediately beneath the product title line, i.e., remove the line space in between these two.

- d. Under CONTRAINDICATIONS, 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. List each contraindication as a bullet.
 - e. Delete (b) (4) from the Patient Information Counseling Statement so that it reads as follows: “**See 17 for Patient Counseling Information and FDA-approved patient labeling.**”
2. Under the FULL PRESCRIBING INFORMATION,
- a. In the Boxed Warning, the phrase (b) (4)
[REDACTED]
 - b. Under **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.
 - c. Under **PATIENT COUNSELING INFORMATION**, insert the text “(Patient Information)” into the reference statement so that it reads as follows: “See FDA-approved patient labeling (Patient Information) (b) (4).”

We request that you resubmit labeling that addresses these issues. The resubmitted labeling will be used for further labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
05/04/2011



NDA 202331

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Takeda Pharmaceuticals North America
One Takeda Parkway
Deerfield, IL 60015

ATTENTION: Beth-Anne Knapp, MBA, RAC
Associate Director, Regulatory Affairs

Dear Ms. Knapp,

Please refer to your New Drug Application (NDA) dated February 21, 2011, received February 24, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azilsartan Medoxomil and Chlorthalidone Tablets, (b) (4) 40 mg/12.5 mg, (b) (4) and 40 mg/25 mg.

We acknowledge receipt of your April 13, 2011 correspondence, on April 13, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary names (b) (4) and (b) (4). This proposed proprietary name request is considered withdrawn as of April 13, 2011.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nina Ton, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Quynh Nguyen at 301-796-0510.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/28/2011

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Proprietary name review

Meeting Date and Time: April 6, 2011, 9:30 AM to 10:00 AM EST
Meeting Location: Teleconference, WO 4322 Bldg 22

Application Number: NDA 202331
Product Name: Azilsartan Medoxomil plus Chlorthalidone
Indication: Hypertension
Sponsor/Applicant Name: Takeda Pharmaceuticals North America Inc.

Meeting Chair: Carol Holquist
Meeting Recorder: Nina Ton

FDA ATTENDEES

Carol Holquist, Director, DMEPA
Zach Oleszczuk, Team Leader, DMEPA
Yelena Maslov, Safety Evaluator, DMEPA
Nina Ton, Safety Regulatory Project Manager, OSE

SPONSOR ATTENDEES

Beth-Anne Knapp, Associate Director, Regulatory Strategy
Katie Clarke, Director, Regulatory Labeling & Operations
Denise Clemons, Director, Marketing

1. BACKGROUND

Takeda submitted a request for the review of the proprietary name (b) (4) on March 3, 2011. The Division of Medication Error Prevention and Analysis (DMEPA) has evaluated the proposed proprietary name and concluded that the name is unacceptable. DMEPA requested a teleconference with the Applicant to discuss safety concerns and provide recommendations.

2. DISCUSSION

DMEPA acknowledged that the Applicant intended the root name (b) (4) to stand for the Azilsartan Medoxomil active ingredient and the modifier (b) (4) as indicated in the submission. However, after reviewing the proposed name (b) (4) DMEPA found the name unacceptable because of the following safety issues identified with the modifier (b) (4)

- The letter string (b) (4) is an abbreviation for pharmaceutical and medical terms such as (b) (4)
- (b) (4) is commonly used throughout literature as an abbreviation for (b) (4)
- The modifier (b) (4) may also be misinterpreted for (b) (4)
- Participants of the study conducted by Addison-Whitney and submitted by Takeda stated that (b) (4). Other participants stated that this letter string does not have any inherent meaning. Additionally, some participants thought that the modifier (b) (4) looks similar to the following (b) (4)
- (b) (4)

DMEPA concluded that the modifier (b) (4) does not have a consistent meaning and this finding is supported by Takeda's study results. DMEPA emphasized that this modifier can be interpreted in many ways.

Takeda asked if most modifiers would cause concerns. DMEPA responded that using a modifier in a proprietary name [REDACTED] (b) (4) would be difficult and would require data to support this strategy.

[REDACTED] (b) (4)

DMEPA discussed the options for a path forward. The first option is to withdraw the proprietary name [REDACTED] (b) (4) and submit a new name. The second option is to wait for the completion of the proprietary name review which should be finished by June 1, 2011.

DMEPA advised Takeda to pursue a naming strategy that did not include a modifier [REDACTED] (b) (4). [REDACTED] DMEPA noted that [REDACTED] (b) (4) should also not be used as part of the new name.

In addition, DMEPA recommended Takeda submit two new names with one being the primary name and one being the alternative name. Takeda asked if the name study should be submitted for the secondary name. DMEPA responded that only the first name is reviewed per guidance. However, submission of a name study for the alternate name would allow DMEPA to provide preliminary comments.

3. ACTION ITEMS

Takeda will withdraw the proposed proprietary name [REDACTED] (b) (4) next week and submit a new name.

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/s/

PHUONG N TON
04/19/2011



NDA 202331

NDA ACKNOWLEDGMENT

Takeda Global Research & Development Center, Inc.
Attention: Beth-Anne Knapp, MBA, RAC
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: TAK-491CLD (azilsartan medoxomil plus chlorthalidone fixed-dose combination) (b) (4) 40/12.5 mg (b) (4) and 40/25 mg

Date of Application: February 21, 2011

Date of Receipt: February 24, 2011

Our Reference Number: NDA 202331

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 25, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
03/02/2011

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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Transmitted via email to: bknapp@tgrd.com

Attention: Beth-Anne Knapp, MBA, RAC

Sponsor: Takeda Global Research & Development Center, Inc.

Phone: (224) 554-2187

Subject: **Pre-NDA Meeting – Clinical and Clinical Pharmacology Preliminary Responses**

Date: November 2, 2010

Pages, including this sheet: 18

From: Quynh Nguyen, Pharm.D., RAC
Phone: 301-796-0510
Fax: 301-796-9838
E-mail: quynh.nguyen@fda.hhs.gov

Please let me know you received this. Thanks!

IND 077278
TAK-491/chlorthalidone
Takeda Global Research & Development Center, Inc.
Pre-NDA Meeting – Clinical and Clinical Pharmacology
Preliminary Responses

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **November 8, 2010** from **11:00 to 12:30 PM ET** between **Takeda Global Research & Development Center, Inc.** and the **Division of Cardiovascular and Renal Products**. We believe that these responses will address all of your questions, and do not feel that a meeting is necessary; however, if there are points that you do not understand or with which you disagree, please advise us, and we will consider your request to hold the meeting.*

DISCUSSION

Clinical Pharmacology

1. The clinical pharmacology program to support the TAK-491CLD NDA includes the TAK-491 studies submitted in the TAK-491 monotherapy NDA (Appendix B), as well as 4 biopharmaceutic studies and a population pharmacokinetics analysis conducted with TAK-491CLD FDC specifically in support of the TAK-491CLD NDA. The phase 1 program was previously agreed to at the November 14, 2007 Pre-IND Meeting. These studies are described in Section 8.1. ***Does the FDA agree that the clinical pharmacology program is adequate support for the marketing application?***

Preliminary Response

We agree.

2. Takeda is planning to utilize the plasma concentration data collected from the 491CLD-302 study as the basis for the population pharmacokinetic analysis and the estimation of mean population pharmacokinetic parameters for TAK-536, TAK-536 M-II, and chlorthalidone, inter-individual variability of the pharmacokinetic parameters, and the variance of the residual error. Intrinsic and extrinsic factors that affect the pharmacokinetics of TAK-536 and chlorthalidone will also be determined. Additionally, the relationship between pharmacokinetics and the primary efficacy endpoint (change from baseline to Week 8 in trough SBP by ABPM) will be evaluated in an exposure-response analysis. ***Does the FDA agree with Takeda's plan for population pharmacokinetics?***

Preliminary Response

We agree.

3. For the TAK-491CLD NDA Modules 2.7.1 and 2.7.2, Takeda plans to present the biopharmaceutic studies and a population pharmacokinetic analysis obtained from the pivotal phase 3 factorial study 491CLD-302. These Module 2 documents will contain cross-references to specific sections of the TAK-491 monotherapy NDA Modules 2.7.1 and 2.7.2, when appropriate, for clinical pharmacology reports utilizing TAK-491 and TAK-536. For balance, Takeda also plans to present relevant chlorthalidone clinical pharmacology data from the full prescribing information and literature. As described in Table 8.a, Takeda plans

to include only the clinical pharmacology reports that are directly supportive of TAK-491CLD in Module 5, with cross-references to the TAK-491 monotherapy NDA 200,796 as appropriate.

(a) Does FDA agree that the planned clinical pharmacology data presentation as described in Section 8.2 for Modules 2.7.1 and 2.7.2 is appropriate and adequate to support the Agency's review of the TAK-491CLD NDA?

Preliminary Response

We agree.

(b) Does FDA agree that it is appropriate to include only the clinical pharmacology reports in which TAK-491CLD was administered in Module 5 of the NDA?

Preliminary Response

We agree.

4. As follow-up to the June 28, 2010 FDA correspondence, Takeda plans to submit the FDA pilot Summary of Clinical Pharmacology for TAK-491CLD NDA 60 days after the original filing to allow for additional analyses. For clinical pharmacology subject matter that is not part of FDC clinical development (eg, metabolism), Takeda plans to cross-reference specific sections of the Summary of Clinical Pharmacology for the TAK-491 monotherapy NDA that was submitted with that NDA's 120-Day Safety Update (NDA 200,796, Amendment 0004, dated August 25, 2010) as well as the full prescribing information and literature for chlorthalidone. ***Does the FDA agree with this cross-reference proposal?***

Preliminary Response

We agree.

Clinical Efficacy

5. For Module 2.7.3 Clinical Summary of Efficacy, Takeda does not plan to integrate the phase 3 studies due to differences in study designs. ***Does the FDA agree that the planned efficacy data presentation described in Section 10.3.1 of the briefing document for Module 2.7.3 Clinical Summary of Efficacy is appropriate and adequate to support the Agency's review of efficacy data for TAK-491CLD?***

Preliminary Response

We agree.

6. Appendix E contains Takeda's current Target Product Profile. Takeda plans to incorporate

(b) (4)



Does the FDA agree that cardiovascular outcome language, as described above and consistent with the draft guidance, can be incorporated in the Indications and Usage and Clinical Studies section of the full prescribing information if the guidance is finalized prior to NDA approval?

Preliminary Response

We agree, and please note that we are awaiting the guidance to be finalized.

7. Following the November 14, 2007, Pre-IND Meeting, FDA provided Takeda with a Points to Consider Document for First Line Therapy. Takeda will include this type of analysis in the phase 3 factorial study 491CLD-302 clinical study report (CSR) and Module 2.7.3. The Indications and Usage section of the full prescribing information will provide estimates of the probability of reaching a blood pressure goal with TAK-491CLD (b) (4) compared to TAK-491 (b) (4) and chlorthalidone (b) (4) monotherapy, or other appropriate FDC dose strength. A description of this analysis is provided in Section 9.1. ***Does FDA agree that pending review of the efficacy and safety data, First Line Therapy could be appropriate in the indication section of the full prescribing information?***

Preliminary Response

We agree.

Clinical Safety

8. As discussed at the November 14, 2007 Pre-IND Meeting and at the May 19, 2009 Type C Meeting, the TAK-491 monotherapy studies that involved coadministration of TAK-491 with chlorthalidone (TAK-491-006, -009, and -016) support the exposure and safety analysis in the TAK-491CLD NDA. Takeda plans on re-submitting phase 1 and 3 CSRs that included TAK-491 co-administered with chlorthalidone and were submitted previously under the TAK-491 monotherapy NDA 200,796. In addition, the TAK-491CLD NDA will cross-reference TAK-491 and TAK-536 CSRs submitted previously under TAK-491 monotherapy NDA 200,796 (see Appendix B). A list of all clinical studies to be included in the TAK-491CLD NDA in Module 5 is provided in Table 7.a, Table 7.b and Table 7.d. ***Does the FDA agree that Takeda's plan for cross-reference and re-submission of clinical study reports submitted to NDA 200,796 will be sufficient for review of the TAK-491CLD NDA?***

Preliminary Response

We agree.

9. For the phase 3 studies, Takeda plans to submit Council for International Organization of Medical Sciences (CIOMS) reports in place of text narratives for deaths and other serious adverse events (SAEs). Programming Assisted Narratives (PANs) will be submitted for premature discontinuations due to adverse events and events of special interest. A sample PAN was submitted to IND 71,867 with the TAK-491 monotherapy pre-NDA briefing document (Serial No. 0181, submitted on September 25, 2009). For phase 1 studies, in-text

narratives in the CSRs will be provided for deaths, other SAEs and discontinuations due to adverse events (AEs). ***Does FDA agree with Takeda's plan for narratives?***

Preliminary Response

We agree.

10. Section 11.9.1 describes Takeda's plan for safety analysis for Module 2.7.4 Clinical Summary of Safety and the Integrated Summary of Safety (ISS). Takeda does not plan to integrate safety data from the Phase 3 studies due to different study designs. In addition, the ISS will not integrate safety data from the phase 1 studies and will only include descriptions of any deaths, other SAEs, and discontinuations due to adverse events from the phase 1 studies. ***Does FDA agree that the planned safety data analysis for Module 2.7.4 and the ISS are adequate to support the FDA's review of safety data for the TAK-491CLD NDA?***

Preliminary Response

We agree.

11. At the May 19, 2009 Type C Meeting, FDA agreed that the estimated safety exposures at the planned filing date were adequate. Current estimates anticipate more than 3177 subjects with hypertension will be exposed to TAK-491CLD, including more than 602 subjects exposed for 6 months and 171 subjects for 12 months. At the time of the 120-Day Safety Update, Takeda anticipates more than 3600 subjects with hypertension will be exposed to TAK-491CLD, including more than 800 subjects exposed for 6 months and 300 subjects exposed for 12 months. ***Does the FDA agree that the long-term patient exposure data to be included in the Original NDA and at the 120-Day Safety Update will adequately support the review of the TAK-491CLD NDA?***

Preliminary Response

We agree.

12. Appendix E contains Takeda's current Target Product Profile. Takeda plans on presenting safety information from the pivotal factorial study 491CLD-302 for the recommended doses (TAK-491CLD (b) (4), 40/12.5, (b) (4) and 40/25 mg) in the Adverse Reactions section of the full prescribing information. In addition, Takeda plans to present safety information from the TAK-491 monotherapy and CLD commercial label that is not covered by TAK-491CLD information. ***Does the FDA agree with Takeda's plan for data presentation included in the Adverse Reactions section of the Target Product Profile?***

Preliminary Response

We agree.

13. For the 120-Day Safety Update, Takeda proposes providing key safety information (deaths, other SAEs, discontinuation due to AEs, and lab values of interest) separately for each of the studies that will be ongoing at the time of the initial NDA: the long-term, open-label safety study 491CLD-308 (Section 9.3), the phase 3 randomized controlled study 491CLD-303 to demonstrate superiority to a comparator (Section 9.4), and the phase 1 BA study 491CLD-106 to compare bioavailability of chlorthalidone from the FDC formulation with an EU-sourced chlorthalidone (Section 8.1).

For the open-label safety study 491CLD-308, an interim report will be submitted with the NDA and only key safety data will be provided in the 120-Day Safety Update; an additional interim CSR will not be provided at that time.

Takeda does not plan on integrating any of these studies with data available at the time of the original filing. Only the datasets in support of the Safety Update will be provided; individual study datasets will not be provided. As in the Original TAK-491CLD NDA, none of the phase 3 study data will be pooled in the Safety Update because of the different study designs and treatment durations. ***Does the FDA agree with Takeda's proposal for the 120-Day Safety Update?***

Preliminary Response

We agree.

General Questions

14. Based on the preliminary efficacy and safety data from the pivotal phase 3 factorial study 491CLD-302 and supportive Phase 3 studies TAK-491CLD-306 and TAK-491CLD-301, summarized in Sections 10.1 and 11.0, Takeda is considering the following doses for registration: TAK-491CLD (b) (4), 40 mg/12.5 mg, (b) (4), and 40/25 mg (see Section 12.0). ***Does FDA have any comments on the preliminary dose selection decision and rationale?***

Preliminary Response

The preliminary dose selection decision and rationale appear reasonable and we will be reviewing your data with the NDA submission.

15. ***Has the FDA identified any issues that could affect the filing of the NDA under 21 CFR 314.101?***

Preliminary Response

No.

16. ***Has the FDA identified any review issues based on the data included in the briefing document?***

Preliminary Response

No.

Data Structure and Format

17. Takeda proposes to provide data listing by CRF domain as appendices to CSRs (ICH E3 guidance, Appendix 16.2) and not provide individual patient profiles (ICH E3 report guidance, Appendix 16.4). SAS datasets containing all individual subject data will be submitted for all studies as SAS transport files (XPT files) per applicable guidance. ***Does FDA agree with Takeda's proposal to submit SAS datasets and not patient profiles in the filing?***

Preliminary Response

We agree.

18. Takeda plans to submit analysis datasets structured according to CDISC ADaM 2.0 model for the TAK-491CLD Phase 3 studies and for the ISS. The Phase 3 analysis data sets will include subject level information, clinical laboratory results, adverse events, vital signs, efficacy endpoints, and ECG, if applicable. The integrated data set files will contain subject level information, all variables used in the integrated analyses, variables used in the calculations of the analysis variables, and other variables as appropriate. The analysis data sets will also be submitted as SAS XPORT transport files. ***Does the FDA agree with the analysis dataset approach for the Phase 3 studies and the ISS?***

Preliminary Response

We agree.

19. SAS XPORT transport files will have no size limit. For each TAK-491CLD clinical study included in the submission, Takeda plans to provide a data definition document (define.xml) that includes metadata information, such as variable name, a description of variable (numeric, character, date, time), codes, and the source of the variable. A blank CRF document annotated to SDTM variables will be included for the TAK-491CLD phase 3 studies. A separate define.pdf document will be provided with each set of analysis datasets for the phase 3 studies and ISS according to CDISC ADaM recommendations. ***Does FDA agree that the planned define file construction and no-limit file size of the transport files are acceptable?***

Preliminary Response

We agree.

20. At the TAK-491 monotherapy Pre-NDA Meeting on October 27, 2009, FDA requested Takeda to submit 'summary level clinical site data for data integrity review and inspection' as part of the pilot program. For the TAK-491CLD NDA, Takeda proposes to provide this dataset in the same format proposed in IND 71,867 (Serial No. 0197 submitted November 23, 2009) and provided in the TAK-491 NDA 200,796 (Serial No. 0000 submitted April 22, 2010). ***Does the FDA agree with this proposal?***

Preliminary Response

We agree. Please see the attached "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" document and the DSI comments document.

Regulatory and Administrative Questions

21. **Full Prescribing Information:** The full prescribing information for TAK-491CLD is based on data from the TAK-491CLD program as well as the commercial labels of TAK-491 and chlorthalidone monotherapy. As the NDA for TAK-491 is under review, the full prescribing information for TAK-491CLD will reflect the full prescribing information for TAK-491 as of January 1, 2011. Any changes or updates to the TAK-491 monotherapy label will be incorporated at the 120-Day Safety Update. ***Does FDA agree with Takeda's plan for updating the full prescribing information?***

Preliminary Response

We agree.

22. **Financial Disclosures:** The NDA for TAK-491CLD will include financial disclosure and certification for all “covered” studies as defined in 21 CFR § 54.2(e). This would include the 3 controlled phase 3 studies (491-301, -302, and -306) for TAK-491CLD as well as the controlled supportive Study TAK-491-009 that was previously provided as part of NDA 200,796 for TAK-491 (azilsartan medoxomil). Financial disclosures or certifications will not be included for Phase 1 studies or Phase 3 open label multicenter studies (491-006, -016, and 491CLD-308), as these studies are not considered “covered” studies per the regulations. *Does the FDA agree with Takeda’s plan for financial disclosure and certification information in the NDA?*

Preliminary Response

We agree.

23. **Pediatric assessment:** Takeda submitted a full waiver for pediatric studies to fulfill the requirements of the Pediatric Research Equity Act (PREA) to IND 77,287 (Serial No. 0125 dated September 21, 2010). *Does the FDA agree with Takeda’s proposed full waiver for pediatric studies to fulfill PREA requirements?*

Preliminary Response

We agree.

Additional Preliminary Responses

Please include the raw data in your NDA submission which you derived your analyses datasets from.

If you have any questions, please call:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Summary Level Clinical Site Data for
Data Integrity Review and Inspection
Planning in NDA and BLA
Submissions

I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Variance (TRTEFFV) – the variance of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Variance (SITEEFFV) – the variance of the site-specific efficacy effect size (SITEEFFE)

-
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
 - Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) – the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR”.

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Summary Level Clinical Site Data Elements

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
IND	IND Number	Num/Char	6 digit identifier	FDA identification number for investigational new drug	010010
TRIAL	Trial Number	Char	String	Study or Trial identification number	ABC-123
SITEID	Site ID	Num/Char	String	Investigator site identification number	50
ARM	Treatment Arm	Num/Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters)	Active (e.g. 25mg), Comparator drug product name (e.g. Drug x), or Placebo
ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site	20
SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site	100
DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site	5
ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application. (limit 200 characters)	Average increase in blood pressure
ENDTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other)	Continuous
TRTEFFR	Treatment Efficacy Result	Num	Floating Point	The efficacy result for each primary endpoint, by treatment arm	0, 0.25, 1, 100
TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm	0, 0.25, 1, 100
SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	The effect size should be the same representation as reported for the primary efficacy analysis	0, 0.25, 1, 100
SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	The variance of the site-specific efficacy effect size (SITEEFFE)	0.065
CENSOR	Censored Observations	Num	Integer	The number of censored observations for the given site and treatment	5
NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site. This value should include multiple events per subject.	10
SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject.	5
DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site	1

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
PROTVIOL	Number of Protocol Violations	Num	Integer	Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject.	20
FINLDISC	Financial Disclosure Amount	Num	Integer	Total financial disclosure amount (\$USD) by the site investigator	50000.00
LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572	Doe
FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572	John
PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator	555-555-5555, 44-555-555-5555
FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator	555-555-5555, 44-555-555-5555
EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator	john.doe@mail.com
COUNTRY	Country	Char	ISO 3166-1-alpha-2	Country in which the site is located	US
STATE	State	Char	String	Unabbreviated state or province in which the site is located	Maryland
CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located	Silver Spring
POSTAL	Postal Code	Char	String	Postal code for the site	20850
STREET	Street Address	Char	String	Street address and office number at which the site is located	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: General Structure of Data Submission Template

IND	TRIAL	SITEID	ARM	ENROLL	SCREEN	DISCONT	ENDPOINT	ENDTYPE	TRTEFFR
000001	Study 1	001	Active	26	61	3	Percent Responders	Binary	0.48
000001	Study 1	001	Placebo	25	61	4	Percent Responders	Binary	0.14
000001	Study 1	002	Active	23	54	2	Percent Responders	Binary	0.48
000001	Study 1	002	Placebo	25	54	4	Percent Responders	Binary	0.14
000001	Study 1	003	Active	27	62	3	Percent Responders	Binary	0.54
000001	Study 1	003	Placebo	26	62	5	Percent Responders	Binary	0.19
000001	Study 1	004	Active	26	29	2	Percent Responders	Binary	0.46
000001	Study 1	004	Placebo	27	29	1	Percent Responders	Binary	0.12

TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	NSAE	SAE	DEATH	PROTVIOL	FINLISC	LASTNAME	FRSTNAME	PHONE
0.0096	0.34	0.0198	NA	0	2	2	0	1	0.00	Doe	John	555-123-4567
0.0049	NA	NA	NA	2	2	2	0	1	0.00	Doe	John	555-123-4567
0.0108	0.33	0.0204	NA	3	2	2	1	0	45000.00	Washington	George	020-3456-7891
0.0049	NA	NA	NA	0	2	2	0	3	45000.00	Washington	George	020-3456-7891
0.0092	0.35	0.0210	NA	2	2	2	0	1	0.00	Jefferson	Thomas	01-89-12-34-56
0.0059	NA	NA	NA	3	6	6	0	0	0.00	Jefferson	Thomas	01-89-12-34-56
0.0095	0.34	0.0161	NA	4	1	1	0	0	0.00	Lincoln	Abraham	555-987-6543
0.0038	NA	NA	NA	1	2	2	0	1	0.00	Lincoln	Abraham	555-987-6543

FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

DSI has 2 types of requests for data to be submitted to the NDA; one type addresses the clinical data submitted in the NDA that will be used for the inspection as background materials (Items I and II) and the other type addresses the site selection process (Item III).

I. Request for general study related information and specific Clinical Investigator information

A. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country, to include contact information (phone, fax, email)

B. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

1. Number of subjects screened for each site by site
2. Number of subjects randomized for each site by site
3. Number of subjects treated who prematurely discontinued for each site by site

C. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:

1. Name, address and contact information of all CROs used in the conduct of the clinical trials
2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

II. Request for Site Level Data

1. For each site in the pivotal clinical trials: Name of primary investigator, accurate address and phone number, e-mail contact
2. For each pivotal trial: Sample blank CRF and case report data tabulations for the site with coding key
3. For each pivotal trial: Site-specific individual subject data (“line”) listings from the datasets:
 - a. Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Line listings by site and subject, of treatment assignment (randomization)

- c. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
- d. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
- e. Line listings by site and subject, of AEs, SAEs, deaths and dates
- f. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
- g. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters or events.
- h. Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
- i. Line listings by site and by subject, of laboratory tests performed for safety monitoring

III. Request for Individual Patient Data Listings format:

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide datasets, as outlined, for each pivotal study submitted in your application.

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

/s/

NORMAN L STOCKBRIDGE
11/02/2010

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

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10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



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Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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Transmitted via email to: bknapp@tgrd.com

Attention: Beth-Anne Knapp, MBA, RAC

Sponsor: Takeda Global Research & Development Center, Inc.

Phone: (224) 554-2187

Subject: **Pre-NDA Meeting – Nonclinical and CMC Preliminary Responses**

Date: September 2, 2010

Pages, including this sheet: 5

From: Quynh Nguyen, Pharm.D., RAC
Phone: 301-796-0510
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Please let me know you received this. Thanks!

IND 077278
TAK-491/chlorthalidione
Takeda Global Research & Development Center, Inc.
Pre-NDA Meeting – Nonclinical and Quality
Preliminary Responses

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **September 9, 2010 from 9:00 to 10:00 AM ET** between **Takeda Global Research & Development Center, Inc.** and the Division of Cardiovascular and Renal Products. We believe that these responses will address all of your questions, and do not feel that a meeting is necessary; however, if there are points that you do not understand or with which you disagree, please advise us, and we will consider your request to hold the meeting.*

DISCUSSION

Nonclinical

1. A full nonclinical development program was conducted in support of the NDA for TAK-491 (NDA 200,796). A total of 11 nonclinical studies (4 PK/absorption, distribution, metabolism, excretion [ADME] and 7 toxicology studies) directly support the TAK-491CLD FDC NDA filing. All reports were filed with NDA 200,796 for TAK-491 monotherapy.

Does the Agency agree that the nonclinical development program for TAK-491CLD, as described in Section 10.0, is sufficient to support the NDA filing for the proposed indication?

Preliminary Responses

Yes, the Division is in agreement with your proposal.

2. Reports for the nonclinical studies supporting the TAK-491CLD FDC NDA were included in Module 4 of the TAK-491 monotherapy NDA and the studies were summarized in the Module 2 summary and overview documents in the TAK-491 NDA (see Appendix A). For the TAK-491CLD NDA, we plan to submit the nonclinical reports (Module 4) and summaries (Module 2) that specifically support the TAK-491CLD FDC and provide cross references to the TAK-491 NDA for the remaining information. To clarify:

(a) Module 4: We plan to submit reports for only the 11 studies that specifically support TAK-491CLD FDC (see Table 10.b), with cross references to the TAK-491 NDA for the remaining reports. Does the FDA concur with this approach?

(b) Module 2: We plan to submit a Pharmacokinetics written summary (Module 2.6.4) and Toxicology written summary (2.6.6), focusing primarily on the 11 studies that specifically support TAK-491CLD FDC. Cross references to the TAK-491 NDA will be included for the Nonclinical Overview (Module 2.4), Pharmacology written summary (Module 2.6.2) and all nonclinical tabulated summaries (Modules 2.6.3, 2.6.5, and 2.6.7). Does the FDA concur with this approach?

Preliminary Responses

Yes, the Division is in agreement with your proposal.

Chemistry, Manufacturing, and Controls

3. For the TAK-491CLD NDA, Takeda would like to cross-reference Sections 2.3.S and 3.2.S to NDA 200,796, which contains information on the TAK-491 drug substance, which is one component of the TAK-491CLD drug product.

(a) Does the FDA agree with Takeda's proposal as described in Section 11.1 to cross reference to NDA 200,796 for the TAK-491 drug substance (Module 2.3.S and Module 3.2.S)?

Preliminary Responses

Yes, the Division is in agreement with your proposal.

For the chlorthalidone component of the TAK-491CLD drug product, Takeda will reference the supplier's DMF for all information on the chlorthalidone drug substance with the exception of a particle size specification that will be included in the TAK-491CLD NDA.

(b) Does the FDA agree with Takeda's proposal as described in Section 11.2 to refer to Ipca DMF (b) (4) for the chlorthalidone drug substance with an additional specification for particle size?

Preliminary Responses

Yes, the Division is in agreement with your proposal. Please include the following information in the NDA:

- a. Complete information for the drug substance manufacturing sites.
 - b. Complete regulatory specification for the drug substance including acceptance limits and test methods.
 - c. Justification for the proposed particle size of chlorthalidone drug substance.
 - d. Description of any analytical procedures used to test the drug substance along with validation data if they are different from the DMF methods.
 - e. Representative COAs for the drug substance batches to be used in the manufacture of the product.
4. At the time of the initial TAK-491CLD NDA filing, Takeda will have stability data through at least 12 months long-term and 6 months accelerated conditions on 3 batches of each strength in each commercial packaging configuration. The batches used for the registration stability studies are representative of the commercial process and scale. Takeda will request an expiry period appropriate for the amount of satisfactory stability data available at the time of the initial filing. At the time of the 120-day safety update, additional stability data will be available. Takeda would like to submit this additional stability data with the 120-day safety update and, assuming the data are satisfactory, propose a longer expiry period.

Does the FDA agree with Takeda's proposal as described in Section 11.4.2 to submit additional stability data in the 120-day safety update with a proposed extension of the expiry period?

Preliminary Responses

Yes, the Division is in agreement with your proposal.

5. The analytical method for TAK-491CLD drug product revealed the presence of an impurity related to the chlorthalidone drug substance (b) (4) that has been identified as a (b) (4). Studies indicate that this impurity is formed as a result of the sample preparation procedure for Takeda's related substances method. Based on this information, and the fact that (b) (4) has not been found to be a degradant or process-related impurity, Takeda proposes to not assign a release specification for (b) (4) and proposes to not include (b) (4) in calculation of total impurities. Takeda will continue to monitor and report the (b) (4) content during registration and post-approval stability studies.

Does the FDA agree with Takeda's proposal as described in Section 11.4.2 to monitor ^{(b) (4)} on registration and post-approval stability testing, but not assign a release specification limit for it and not include it in the calculation of total impurities?

Preliminary Responses

Yes, the Division is in agreement with your proposal.

If you have any questions, please call:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77278	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	TAK 491/CHLORTHALIDONE

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/s/

NORMAN L STOCKBRIDGE
09/02/2010

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

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Transmitted via email to: bknapp@tgrd.com

Attention: Beth-Anne Knapp, MBA, RAC

Sponsor: Takeda Global Research & Development Center, Inc.

Phone: (847) 582-3507

Subject: **Type C Guidance Teleconference Minutes**

Date: May 17, 2010

Pages, including this sheet: 7

From: Quynh Nguyen, Pharm.D., RAC
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Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Type C Guidance Meeting via Teleconference with Sponsor

Application Number: IND 077278
Sponsor: Takeda Global Research & Development Center, Inc.
Drug: TAK-491/chlorthalidone
Type of Meeting: Guidance
Classification: C
Meeting Date: April 27, 2010
Briefing Package Received: April 16, 2010
Confirmation Date: April 20, 2009
Meeting Request Received: April 16, 2009
Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Recorder: Quynh Nguyen, Pharm.D., RAC

List of Attendees:

Food and Drug Administration

Office of New Drugs, Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director
Thomas Marciniak, M.D.	Medical Team Leader
Maryann Gordon, M.D.	Medical Officer
Quynh Nguyen, Pharm.D., RAC	Regulatory Health Project Manager

Office of Biostatistics, Division of Biometrics I

James Hung, Ph.D.	Director
Jialu Zhang, Ph.D.	Statistician

Takeda Global Research & Development Center, Inc.

Charlie Cao, Ph.D.	Associate Director, Analytical Sciences
Beth-Anne Knapp	Manager, Regulatory Strategy
Stuart Kupfer, M.D.	Executive Medical Director, Clinical Science
Binita Kwankin	Director, Regulatory Strategy
Eric Lloyd	Principal Statistician, Analytical Sciences

BACKGROUND

TAK-491/chlorthalidone (CLD) is a fixed-dose combination product of TAK-491, an angiotensin II receptor blocker, plus CLD, a thiazide-type diuretic. Takeda is developing TAK-491/CLD for the treatment of moderate to severe hypertension. The sponsor requested this Type C Guidance meeting to clarify the Division's written response dated March 30, 2010. The Division's written response provided comments on the sponsor's January 13, 2010 submission containing a statistical analysis plan in support of the secondary endpoints for analyses of the Black subgroup in Study TAK-491CLD_302, as well as a desired labeling claim pertaining to Black patients. The Division's Preliminary Responses for this meeting were sent to the sponsor on April 22, 2010. Based on their understanding of the Division's Preliminary Responses, the sponsor submitted a proposed analysis on April 26, 2010 (see attachment) on which they were seeking agreement during the meeting. Only Clarification Question 1 was discussed as noted below.

DISCUSSION

Clarification Question 1

In the response dated March 30, 2010, FDA recommends an alternative approach to demonstrate the efficacy of TAK-491CLD FDC [for the overall population for registration] by showing that TAK-491CLD FDC 80 mg/12.5 mg is significantly better than both TAK-491CLD 80 mg/P.mg and TAK-491CLD P.mg/25 mg, with the assumption that a dose-response relationship is also demonstrated. At the November 14, 2007 Pre-IND Meeting (Meeting Minutes), it was Takeda's understanding that the currently proposed analysis for Study TAK-491CLD_302 as specified in the SAP would be an acceptable approach for registration.

Takeda would like to clarify whether:

a) the pooling strategy discussed in the Pre-IND meeting and proposed in the SAP is not acceptable for registration?

b) the traditional statistical approach employed in past approvals in which the FDC is compared to its respective components for the overall population or the Black patient subgroup is not acceptable?

Preliminary Responses

It is not acceptable to pool the two high-dose monotherapy arms. You may pool any combination of the arms that receive both TAK491 and CLD. You must then distinguish the TAK-491/CLD arm or pooled arms from each of the two high-dose monotherapy arms.

If you refer to the AVE test proposed by Hung et al., the Division no longer recommends the use of that method as the primary end point. We take a more informal approach to assessing dose-response.

Discussion during Meeting

Dr. Stockbridge began the teleconference by noting that the Division was generally nervous about changes made to the statistical analysis plan (SAP) after a large fraction of the data have been collected. He indicated that although the sponsor's proposed analysis dated April 26, 2010 was viable, the Division would be extremely uncomfortable if the only successful analysis is the one crafted other than the previously defined analysis. The sponsor acknowledged this and confirmed that their study was ongoing. The sponsor further explained that during the May 19, 2009 Type C Meeting, they had stated that TAK-491_CLD could probably have a greater benefit and a lower risk for Black patients to which the Division had suggested that the Division could review the SAP to see if the sponsor could obtain a labeling claim. Thus, the sponsor subsequently submitted to the Division their SAP and Request for Scientific Advice dated January 13, 2010.

Dr. Hung clarified the pooling strategy with the sponsor. The sponsor confirmed that they would not pool the combination arms at the patient level. The sponsor will combine the treatment estimates of the combination arms using a contrast statement in SAS and compare with the highest dose of the monotherapies. This was acceptable to the Division.

Regarding the labeling, Dr. Stockbridge clarified that the data would not result in a separate claim for use in the Black subgroup, but the label would describe qualitatively and quantitatively the effect in the Black population. The sponsor confirmed their understanding of this and indicated that it was not their intent to seek an explicit claim for use in Black patients. Dr. Stockbridge added that even without a hypothesis test, the results from a pre-specified subgroup analysis of Black patients would be described in the labeling. The Division confirmed that it was not necessary for the sponsor to control for Type 1 error for subgroup analyses of Black patients or any other subgroup (e.g., patients > 65 and < 65 years old; males and females). This would also not preclude a description of the analyses of these subgroups in the labeling.

Clarification Question 2

If the statistical approach proposed in the SAP is not acceptable, as discussed in Clarification Question 1, Takeda would appreciate clarification based on the following feedback:

a) the Agency requests that *'some dose of the combination is [has to be] significantly better than the highest dose of each component'* (in the response dated March 30, 2010)

and

b) the Agency requests that *'the key comparison is that the highest dose combination (80/25) must beat the respective components'* (FDA's response for Question 2 of November 14, 2007Pre-IND Meeting)

Based on Takeda's understanding of this feedback, the primary comparison is to show that TAK-491CLD FDC 80 mg/25 mg is significantly better than both TAK-491CLD 80 mg/P.mg and TAK-491CLD P.mg/25 mg from an analysis of covariance (ANCOVA) model with treatment as a factor and baseline as a covariate on change from baseline to Week 8 in trough SBP by ABPM. Within the framework of ANCOVA, other cell by cell comparisons to their respective monotherapy components will be performed without type 1 error control. If significance for other individual FDC doses based on a nominal p-value is demonstrated and a dose-response relationship is established, this would qualify various FDC doses for approval for the given patient population.

Is Takeda's understanding correct?

Preliminary Responses

Yes, you are correct that if you show that TAK-491CLD FDC 80 mg/25 mg is significantly better than its monotherapy components, you do not have to control type I error for other cell comparisons. You are not required to use the highest dose combination as long as you make the primary comparison to the highest dose monotherapy (TAK-491 80 mg and CLD 25 mg). For example, you may pool several doses of combination for the comparison, or you may choose a different dose other than the highest dose combination. A common practice is to compare the highest dose combination to the highest dose monotherapy components. You may wish to consider not using a balanced factorial design but to have larger sample sizes for the high dose monotherapy and the high dose combination cells.

Clarification Question 3

Takeda would like to clarify whether the approach described below would support the proposed claim for the Black patient population?

For the Black patient population, Takeda would perform formal testing and control for overall study Type 1 error by using a step-wise testing procedure on the primary efficacy endpoint on TAK-491CLD FDC (80 mg/25 mg) and its respective monotherapy components in the overall patient population followed by Black patient population (TAK-491CLD FDC 80 mg/25 mg). The ANCOVA model specified in Clarification Question 2 will be used for the overall patient population. Statistical significance will only be tested in the Black patient population (dataset with only Black patients) if TAK-491CLD 80 mg/25 mg beats both respective monotherapy components in the overall patient population first.

Preliminary Responses

We would plan to include the results (point estimates and confidence intervals) of the comparisons in Blacks of the 80 mg/25 mg combination to the high dose monotherapies in labeling if you include sufficient numbers of Blacks in the planned study to have some confidence in the results. Whether the results support a simple claim of effectiveness in Blacks depends upon the robustness of the results.

Please note that we consider the critical comparisons for the subgroup analyses in Blacks, as well as for the study as a whole, to be comparisons of a combination group to the high dose monotherapies.

Additional Clarification from Takeda for the first key secondary endpoint:

The Agency also commented 'that the first key secondary endpoint is still a measurement of blood pressure in the ITT population and should be removed from the sequential testing chain'. This endpoint was elevated to the first key secondary endpoint in the protocol in response to the CHMP's focus on clinic BP for registration in Europe. The first key secondary endpoint (change from baseline to Week 8 in trough, sitting, clinic SBP) will not be included in the sequential testing chain for the primary endpoint; however, the same approach for type 1 error control for the primary endpoint will be applied to the first key secondary endpoint.

Preliminary Responses

We agree with your clarification. Please note that you do not need to use the same SAP in the US as you are using for registration in Europe.

CONCLUSION

This meeting was scheduled to clarify the Division's written comments dated March 30, 2010 regarding the sponsor's January 13, 2010 SAP for Study TAK-491CLD_302 regarding the Black subgroup and proposed labeling claim. During the meeting, agreement was reached regarding the sponsor's pooling strategy. The labeling strategy was also clarified.

Minutes preparation: Quynh Nguyen, Pharm.D., RAC

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Rd:

N Stockbridge 5-10-10
T Marciniak 5-10-10
M Gordon 5-7-10
J Hung 5-7-10
J Zhang 5-7-10

Attachment: Takeda's Proposed Analysis dated April 26, 2010 in Response to Division's Preliminary Responses

Takeda would like to thank the Agency for their clear and helpful feedback dated March 30, 2010, and April 22, 2010, to the request submitted January 13, 2010 (Serial No. 0084) and clarification questions dated April 16, 2010 (Serial No. 0096).

Based on Takeda's understanding of the totality of the Agency's feedback, Takeda would like to propose the following analysis plan. In the April 27, 2010, teleconference, we'd like to confirm whether the proposal is acceptable. The amended protocol and statistical analysis plan will be submitted within the next few weeks.

1. The primary comparison will be to show that the pool of the TAK-491CLD FDC 40 mg/25 mg cell and TAK-491CLD FDC 80 mg/25 mg cell is significantly better than the individual TAK-491CLD 80 mg/P.mg cell and the TAK-491CLD P.mg/25 mg cell (high dose monotherapies) from an analysis of covariance (ANCOVA) model with treatment as a factor (11 arms) and baseline as a covariate on change from baseline to Week 8 in trough SBP by ABPM. The LS mean of the pool (TAK-491CLD FDC 40 mg/25 mg cell and TAK-491CLD FDC 80 mg/25 mg cell) will be obtained by using a contrast statement from the ANCOVA model.
2. Within the framework of ANCOVA, all FDC cell by cell comparisons to their respective monotherapy components will be performed without type 1 error control. If significance for individual FDC doses compared to their respective monotherapy components based on a nominal p-value is demonstrated and a dose-response relationship is established, this will qualify various FDC doses for approval for the given patient population.
3. For the Black patient population, Takeda will perform formal testing and control for overall study two-sided Type 1 error of 0.05 by using a step-wise testing procedure on the primary efficacy comparison (as described in number 1 above) in the overall patient population followed by the Black patient population.

Of note, we expect 19-20% of the overall patient population to be Black. The treatment difference for trough SBP by ABPM in co-administration of TAK-491 and chlorthalidone (CLD) compared with CLD alone was more than 11 mmHg [Study TAK-491-009 conducted under IND 71,867 (TAK-491)].

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77278	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	TAK 491/CHLORTHALIDONE

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/s/

NORMAN L STOCKBRIDGE
05/17/2010

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Transmitted via email to: dyarbrough@tgrd.com

Attention: Ms. Deborah Yarbrough

Sponsor: Takeda Global Research & Development Center, Inc.

Phone: (847) 582-3511

Subject: **Type C Guidance Meeting Minutes**

Date: June 22, 2009

Pages, including this sheet: 13

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Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Type C Guidance Meeting with Sponsor

Application Number: INDs 71,867 and 77,278
Sponsor: Takeda Global Research & Development Center, Inc.
Drug: TAK-491 and TAK-491/chlorthalidone (CLD)
Type of Meeting: Guidance
Classification: C
Meeting Date: May 19, 2009
Briefing Package Received: April 17, 2009
Confirmation Date: March 9, 2009
Meeting Request Received: March 2, 2009
Meeting Chair: Norman Stockbridge, MD, PhD
Recorder: Quynh Nguyen, PharmD, RAC

List of Attendees:

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Norman Stockbridge, MD, PhD	Director, Division of Cardiovascular and Renal Products (DCRP)
Thomas Marciniak, MD	Medical Team Leader, DCRP
Melanie Blank, MD	Medical Officer, DCRP
Phillip Gatti, PhD	Pharmacologist, DCRP
Quynh Nguyen, PharmD, RAC	Regulatory Health Project Manager, DCRP

Takeda Global Research & Development Center, Inc.

Karen Asin, PhD	Director, Pharmacology
Bruce Barger, DO	Associate Medical Director, Pharmacovigilance
Guoliang "Charlie" Cao, PhD	Associate Director, Biometrics and Data Management
Rosemarie Green, RPh	Asst. Project Director, Strategic Project Management
Akira Kondo	Affiliate, Clinical Science
Beth-Anne Knapp, MBA RAC	Product Manager, Regulatory Affairs Strategy
Stuart Kupfer, MD	Executive Medical Director, Clinical Science
Binita Kwankin	Director, Regulatory Affairs Strategy
Mitchell Friedman, PhD	Director, Toxicology
Fiona Mortimer	Associate Director, EU Regulatory Affairs
Stuart Levin, PhD	Director, Pathology

(b) (4)

(b) (4)

Deborah Yarbrough, MS, MBA	Manager, Regulatory Affairs Strategy
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BACKGROUND

TAK-491 is a prodrug that is hydrolyzed rapidly and completely to the active moiety, TAK-536, an angiotensin AT₁ receptor antagonist. The proposed indication is for the treatment of hypertension.

TAK-491/CLD is a fixed-dose combination (FDC) being developed in part because the sponsor believes this combination has the potential to provide substantially greater antihypertensive efficacy compared with other similar, currently available dual antihypertensive FDCs. This Type C Guidance meeting was scheduled to discuss emerging serum creatinine, blood pressure, and other data in the TAK-491 Phase 3 program and the impact of these data on the TAK-491 and TAK-491/CLD proposed NDA submissions. The Division's Preliminary Responses were sent to the sponsor on May 13, 2009. The sponsor agreed with the Division's Preliminary Response to Question 1; therefore, only Questions 2 and 3 were discussed as noted below.

DISCUSSION

Question 1:

In clinical studies in which TAK-491 has been coadministered with chlorthalidone 25 mg, the frequency of creatinine elevations has been higher than that observed with TAK-491 alone or with TAK-491 coadministered with amlodipine. Evaluation of preliminary clinical data indicates that the pattern of creatinine elevations observed during coadministration of TAK-491 with chlorthalidone 25 mg is consistent with pharmacological effects rather than structural nephrotoxic effects. In TAK-491 and TAK-536 monotherapy studies, elevations greater than 30% were infrequent and did not occur in excess during treatment with TAK-491 relative to placebo or the active comparator olmesartan (Studies 01-05-TL-491-005 [491-005], 491-008, and 01-03-TL-536-002 [536-002]). Similarly, creatinine elevations were uncommon when TAK-491 was coadministered with amlodipine 5 mg (Study 491-010). In contrast, acute increases in creatinine levels were observed in some subjects in the chlorthalidone 25 mg coadministration studies and were accompanied by much greater reductions in blood pressure, as well as an increase in blood urea nitrogen (BUN) to creatinine ratio, suggesting an element of volume depletion. Importantly, data from individual subjects with follow-up measurements in the chlorthalidone coadministration studies demonstrate that creatinine elevations were reversible and that creatinine levels returned toward baseline values after discontinuation of study drug. These findings are consistent with the characteristic decrease of intraglomerular pressure associated with renin-angiotensin-aldosterone system (RAAS) blockade, which likely is exaggerated by the decreased renal perfusion associated with the potent blood pressure reductions and diuretic effects of chlorthalidone 25 mg.

In summary, based on the time course of creatinine elevations, associated blood pressure reductions, and reversibility after study drug discontinuation that have been observed in clinical trials (reviewed in Section 4.0 of the briefing document), as well as supportive data from nonclinical studies (Section 3.0 of the briefing document), TGRD believes that the serum creatinine elevations observed in some subjects receiving TAK-491 coadministered with chlorthalidone 25 mg is a pharmacologic response to RAAS blockade in the setting of potent diuresis and extensive blood pressure reduction, rather than a toxicologic effect.

Does the Agency concur that the data presented in the briefing document support this interpretation?

Preliminary Response

We concur that the data are consistent with your hypothesis.

Question 2:

In response to the observed serum creatinine elevations, TGRD has modified the TAK-491 and

TAK-491CLD programs as precautionary measures to assure subject safety and to better characterize this pharmacodynamic effect by incorporating investigator guidance, subject monitoring, and study design revisions. These changes include:

- a) Addition of guidance to investigators regarding management of serum creatinine elevations, with instructions to closely monitor and consider discontinuing subjects whose serum creatinine increases from baseline are greater than 30% and exceed the upper limit of normal (ULN) (Section 5.2.1 of the briefing document). On the basis of additional clinical data (incidence of creatinine elevations and their reversibility) and nonclinical data (absence of a nephrotoxic effect) have become available, TGRD is planning to raise the threshold for discontinuation to serum creatinine increases from baseline greater than 50% and above the ULN. Subjects whose serum creatinine increases by 30 to 50% and exceeds the ULN, but remains stable, will remain on study drug and continue to be monitored closely.
- b) Study design modifications to the TAK-491 monotherapy program to further characterize the effects of TAK-491 and diuretic coadministration on serum creatinine levels by coadministering TAK-491 and the less potent diuretic, HCTZ. These changes include enrollment of additional subjects into the long-term, open-label safety study (491-006) and addition of an open-label extension to the double-blind comparator study (491_301). These subjects will receive open-label TAK-491 with HCTZ as rescue if needed to achieve blood pressure targets (Section 5.2.2 of the briefing document).
- c) A 1-year, open-label safety study (491CLD_308) was added to the TAK-491CLD FDC program to more fully characterize the long-term safety and tolerability of the FDC. Additionally, consistent with clinical management of hypertension, a “treat-to-target blood pressure” design was incorporated into most studies in the TAK-491CLD FDC program such that all subjects are initiated on a low dose of the TAK-491CLD FDC (TAK-491 20 mg or 40 mg plus a low dose of chlorthalidone 12.5 mg). Subjects are titrated to higher doses of the TAK-491CLD FDC only if they fail to achieve prespecified blood pressure targets. These and additional modifications that have been made to the TAK-491CLD FDC development program are summarized in Section 6.2 of the briefing document.

Does the Agency agree that these program modifications are appropriate to better characterize this pharmacodynamic effect in support of the NDAs for TAK-491 and 491CLD FDC?

Preliminary Response

We have renal safety concerns about your TAK-491 + chlorthalidone combination product.

We recommend that you make the following modifications to your development plan:

- Add a control group to your long term safety study. We would be happy to discuss with you the possibilities for the control group and whether any additional claims are possible if you decide to include more than one control group.
- Include patients with eGFR of <50 mL/min to assess the risk of adverse renal effects in a more vulnerable population.
- Monitor for albuminuria, at baseline and at monthly intervals during your long term study as this may be a marker of acute kidney injury.
- Consider testing the effects of TAK-491 with the biomarker of tubular injury, KIM-1. Although we do not fully understand how to interpret these values in clinical study applications, it would be helpful from our perspective to understand the effects of TAK-491 +/- chlorthalidone on this biomarker that may one day prove to be reflective of acute tubular injury in humans. If you are interested in this suggestion, please contact [REDACTED] (b) (4)
- Enroll a sufficient number of black patients so that you can assess if there are racial differences in the risk for developing irreversible changes in serum creatinine.

Discussion during Meeting

Renal safety concerns

The sponsor asked for clarification regarding the phrase “renal safety concerns” in the Division’s Preliminary Response. Dr. Stockbridge clarified that the sponsor will need to show due diligence in their development program to provide reassurance about the likely interpretation and hypothesis that the serum creatinine elevations observed in some subjects receiving TAK-491 coadministered with chlorthalidone 25 mg is a pharmacologic response to RAAS blockade, i.e., a result of hemodynamic effects, in the setting of potent diuresis and extensive blood pressure reduction, rather than a toxicologic effect..

Addition of control group

The sponsor asked for clarification on the Division’s recommendation to add a control group to the long-term safety study. Dr. Marciniak explained that while outcome studies done with CLD are associated with good cardiovascular outcome data in the U.S., hydrochlorothiazide (HCTZ) is the predominantly used diuretic. The question that remains is whether HCTZ is also associated with an improvement in cardiovascular outcomes. It is also important to understand if the serum creatinine elevations are due to chlorthalidone alone or if there is a unique effect of TAK-491 in the TAK-491 plus chlorthalidone fixed-dose combination. Additionally, it is important to understand what the effects of the combination drug on serum potassium are compared to each drug when given alone. The addition of both a HCTZ and a CLD control group would help determine if there are detectable differences in serum creatinine and potassium effects between long-term HCTZ use and CLD use.

The sponsor commented that if they added CLD alone as a control group in their long-term study, then they would likely have to add other antihypertensive agents, which might confound the study. Dr. Marciniak acknowledged that the interpretation could be confounded, but the trade-off would be that the sponsor could receive a possible labeling claim from the results of a comparative study. Dr. Marciniak emphasized that using either CLD alone or HCTZ as a comparator in a long-term study would be extremely useful for establishing whether or not there is a renal safety problem with the combination drug compared to the diuretic alone.

The sponsor agreed that it was reasonable to include a comparator in the long-term study and stated that a Benicar HCT (olmesartan medoxomil/HCTZ) comparator was being considered. The sponsor asked whether it would be acceptable to have ratios that were not 1:1 if using multiple comparators, e.g., a 2:1 randomization of TAK-491/CLD to comparator. The Division accepted that event rates rather than numbers would be compared and agreed that unequal randomization is acceptable. In addition, the study duration of 6-months to one year would be acceptable. The sponsor stated that they will submit a revised study for the Division’s review.

NDA overview for TAK-491/CLD

The sponsor discussed the status of their clinical studies and plans for NDA filing for the TAK-491/CLD FDC product (see attached slides). The sponsor commented that the dilemma was that they planned not to have the combination long-term safety study completed at the time of the NDA filing for the monotherapy, TAK-491. The sponsor discussed their estimated TAK-491/CLD exposures at 6 months and 12 months based on a re-design of the long-term safety study, including a comparator. The Division indicated that if the data are supportive of the hypothesis, then the exposures presented should be sufficient.

Inclusion of patients with eGFR <50 mL/min

The sponsor agreed with the Division’s recommendation to include patients with eGFR <50 mL/min and clarified that all studies are enrolling patients with eGFR of <50 mL/min but >30 mL/min.

Monitoring for albuminuria

The sponsor plans to monitor for albuminuria as suggested by the Division. However, instead of monitoring at monthly intervals, they plan to monitor every month for the first six months only and every other month thereafter. The Division agreed that this was acceptable.

Testing effects of TAK-491 with KIM-1

Dr. Blank explained that KIM-1 is not thought to increase with hemodynamic effects, only with renal injury. Therefore if KIM-1 were shown to be unchanged in patients on TAK-491, this would be reassuring. Dr. Stockbridge added that this biomarker information would be quite useful in determining whether the renal effects were due to toxic effects of TAK-491 or not. The sponsor pointed out that it would be difficult to validate however and asked whether a small, nested substudy would be acceptable. Dr. Blank suggested that the sponsor contact Dr. (b) (4) about storing samples or studying KIM-1 only in those patients who had increased creatinine levels. The sponsor stated that they would consider measuring KIM-1 in their program, but they had reservations because the biomarker has only been qualified in non-clinical studies and not clinical studies. The sponsor did contact Dr. (b) (4) and they stated that they would follow up with him again.

Enrollment of black patients

The sponsor stated that they have already enrolled black patients and they have a special population study dedicated to black subjects only. The total number of black patients enrolled in the program is 15-20%. In the long-term study, they are about 33% black patients. The Division agreed that the number of black patients was sufficient and would give a sense of whether they were any angioedema issues.

The sponsor asked for clarification regarding the phrase “risk for developing irreversible changes in serum creatinine” in the Division’s Preliminary Response. Dr. Blank explained that there is possibly more volume depletion with CLD and the hemodynamic effects could be different, so the Division would want to understand if there are differences between Caucasian and black patients. The sponsor stated that they believed that black patients who are mostly volume overloaded would probably have a greater benefit and a lower risk than the Caucasian population from the combination drug. After establishing that the sponsor was in the early stage of enrollment for their factorial study, Dr. Stockbridge suggested that they could review their statistical analysis plan (SAP) to see if they could obtain a claim, e.g., by increasing the number of black patients in the trial and testing for a subsidiary hypothesis. The number of black patients needed, however, would be driven by the effect size. The sponsor stated that they would review their study to see if it is sufficiently powered. Dr. Marciniak added that it might be possible for the sponsor to obtain a labeling claim based on doing the subsidiary analysis.

Management of serum creatinine elevations

The sponsor proposed changing the discontinuation criteria based on serum creatinine from >30% and >ULN to >50% and >ULN (see Question 2a). Subjects would continue to be carefully monitored based on the protocol-specified guidance for investigators. The Division agreed that this was acceptable. It was also suggested that the sponsor consider whether the rise or change in serum creatinine after week 2 or 4 may also be incorporated into the withdrawal criteria and whether changes in eGFR may be better indicators than serum creatinine. The sponsor responded that the original withdrawal criteria were developed after discussion with advisors on eGFR versus serum creatinine, and that serum creatinine was selected based on the historical source data behind the NKF guidance. The Division indicated that the use of eGFR versus serum creatinine was the preferred choice, particularly for defining the population of patients with baseline renal disease.

Question 3:

As referenced above in Question 2, TGRD has modified the clinical development programs by supplementing the extent of long-term exposure. The estimated exposures for each program are summarized in Section 7.0 of the briefing document.

Does the Agency consider that these estimated exposures will be adequate to characterize the safety of TAK-491 in support of the NDAs for TAK-491 and TAK-491/CLD FDC?

Preliminary Response

See above Preliminary Responses to Question 2.

Discussion during Meeting

The Division agreed that an expected exposure of over 4000 patients in the TAK-491 program and over 3000 patients in the TAK-491/CLD program is reasonable for NDA filing.

Other Issues Discussed during Meeting

Superiority claim over Benicar HCT

The sponsor indicated their interest in pursuing a superiority labeling claim for TAK-491/CLD to Benicar HCT. Dr. Stockbridge noted that such a claim would be extremely unusual since there were no other comparative effectiveness claims versus a combination product.

Dr. Stockbridge outlined the basic principles for a superiority claim for a monotherapy-to-monotherapy comparison as follows:

- Need a robust demonstration of superiority on the measure of interest, meaning two trials are usually required.
- Agents compared must be in the same class.
- Comparison needs to be “fair,” i.e., the comparator drug should be used at least as well as the label says, i.e., optimally dosed.

Dr. Marciniak commented that there is good data regarding trough blood pressure in angiotensin receptor blockers (ARBs) and he thought if the sponsor’s drug were to beat Benicar HCT, then it might be possible to receive a claim against all the ARBs. Dr. Stockbridge said this issue could be considered, but the Division would have to review the argument that the sponsor chose an ARB comparator that at its highest dose is at least as good as all the other ARBs. The sponsor stated that they have some Phase 2 data already showing that TAK-491 had statistically significant better reductions in blood pressure compared to olmesartan.

The Division stated that a superiority claim for monotherapy was more straightforward and that superiority in monotherapy would not carry over to the fixed-dose combination. Also, trough blood pressure changes are similar for all ARBs. Dr. Stockbridge added that except for losartan, the highest approved doses of ARBs produce similar blood pressure effects at peak and trough and that purely increasing the dose does not increase the effect. Therefore, working on the same system is not likely to produce a greater decrease in blood pressure. The sponsor stated that preliminary data suggests that TAK-491 is superior to other ARBs.

The Division encouraged the sponsor to submit a Special Protocol Assessment containing their trial protocol, SAP, proposed labeling claims, and questions to the Division for their combination study for superiority since this would need to be discussed further with the Office Director.

INDs 71,867 and 77,278
TAK-491 and TAK-491/CLD
Takeda
Page 8 of 13

Minutes preparation: Quynh Nguyen, PharmD, RAC

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, MD, PhD

Rd:
N Stockbridge 6/19/09
T Marciniak 6/19/09
M Blank 6/19/09
P Gatti 6/19/09

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Linked Applications	Sponsor Name	Drug Name / Subject
IND 71867	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	TAK-491
IND 77278	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	TAK 491/CHLORTHALIDONE

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

/s/

NORMAN L STOCKBRIDGE
06/22/2009

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
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Transmitted via email to: gharris@tgrd.com

Attention: Dr. Gloria Harris

Sponsor: Takeda Global Research & Development
Center, Inc.

Phone: (224) 554-5367

Subject: Pre-IND Meeting Minutes

Date: February 7, 2008

Pages, including this sheet: 13

From: Quynh Nguyen, Pharm.D.

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Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Pre-IND Meeting with Sponsor

Application: Pre-IND 77,278

Sponsor: Takeda Global Research & Development Center, Inc. (TGRD)

Drug: TAK-491/chlorthalidone (CLD) fixed dose combination (FDC)

Type of Meeting: Pre-IND
Classification: B

Meeting Date: November 14, 2007
Briefing Package Received: October 12, 2007
Confirmation Date: September 19, 2007
Meeting Request Received: September 6, 2007

Meeting Chair: Robert Temple, M.D.
Recorder: Quynh Nguyen, Pharm.D.

List of Attendees:

Food and Drug Administration

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D.	Director, Division of Cardiovascular and Renal Products (DCRP)
Ellis Unger, M.D.	Deputy Director, DCRP
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, DCRP
Akinwale Williams, M.D.	Medical Officer, DCRP
James Hung, Ph.D.	Director, Division of Biometrics I
Jialu Zhang, Ph.D.	Statistician, Division of Biometrics I
Peter Hinderling, M.D.	Clinical Pharmacologist, Office of Clinical Pharmacology
Donald Jensen, D.V.M.	Pharmacologist, DCRP
William Link, Ph.D.	Pharmacologist, DCRP
Edward Fromm, R.Ph.	Chief, Project Management Staff, DCRP
Anna Park-Hong, R.Ph.	Regulatory Health Project Manager, DCRP
Quynh Nguyen, Pharm.D.	Regulatory Health Project Manager, DCRP

Takeda Global Research & Development Center, Inc.

Alfonso Perez, M.D.	Vice President, Clinical Research
Stuart Kupfer, M.D.	Senior Medical Director, Clinical Research
Guoliang "Charlie" Cao, Ph.D.	Senior Manager, Biometrics and Data Management
Rosemarie Green, R.Ph.	Senior Project Manager, Project Management
Akira Kondo	Strategic Development Department, Takeda Pharmaceutical Co.
Deborah Yarbrough, M.S., M.B.A.	Program Manager, Regulatory Affairs
Fiona Mortimer	Program Manager, Regulatory Affairs
Ingrid Hoos	Regulatory Affairs Consultant

BACKGROUND

TAK-491 is being developed for the treatment of hypertension and is a prodrug that is hydrolyzed completely to the active moiety, TAK-536, an angiotensin II AT₁ receptor antagonist (IND (b) (4)). TAK-491/chlorthalidone (CLD) fixed-dose combination is being developed for the treatment of hypertension, including initial treatment in patients with moderate to severe hypertension. This Pre-IND meeting was scheduled to discuss the proposed Phase 3 clinical development plan for TAK-491/CLD. The Division's Preliminary Responses were sent to the sponsor on November 9, 2007. The sponsor agreed with the Division's Preliminary Responses to Question 2b, sub-bullets 1 and 3, and 3a. The purpose of this meeting was to clarify the Agency's comments on Questions 1a, 1b, 2 and 3 as noted below.

DISCUSSION

Question 1

- a.) *Does the Agency agree that the study designs and overall patient exposure are adequate to fully characterize the safety and efficacy of TAK-491/CLD?*
- b.) *Provided that the study outcomes are positive, does the Agency agree that the studies listed here are adequate to support the proposed indication?*

The phase 3 clinical development plan consists of the following two studies:

Factorial Study of FDC formulation (TAK-491CLD_302)

- 2 week single-blind placebo run-in/washout followed by a 6 week double-blind treatment period.
- Subjects with mild, moderate, or severe essential hypertension.
- 11 treatment groups:

		TAK-491			
		Placebo	20 mg	40 mg	80 mg
CLD	Placebo	--	x	x	x
	12.5 mg	x	x	x	x
	25 mg	x	x	x	x

TAK-491/CLD FDC vs. TAK-491 Monotherapy Comparator Study (TAK-491CLD_304)

- 2 week single-blind placebo run-in/washout followed by a 6 week double-blind treatment period.
- Subjects with moderate or severe hypertension.
- 2 treatment groups:

Treatment Group	Initial Dose	Forced Dose Titration After Week 2
TAK-491	40 mg	80 mg
TAK-491/CLD FDC	40/12.5 mg	80/25 mg

Complete study designs are presented in Section 4.4.2.

Based on previous agreement with the Agency at the TAK-491 EOP1 meeting, the factorial study (TAK-491CLD_302) will be the core efficacy and safety study in the TAK-491/CLD development program to support the hypertension indication. The primary objective of this study is to determine if the

TAK-491/CLD FDC treatment groups, in aggregate, reduce blood pressure more effectively than either the TAK-491 treatment groups or the CLD treatment groups alone in patients with mild, moderate, or severe hypertension (clinic systolic blood pressure [SBP] 150-190 mm Hg and 24-hour mean SBP 130-170 mm Hg). Secondly, the study is designed to determine if the six individual drug combinations lower blood pressure more effectively than either monotherapy alone at their respective dose strengths. Another major objective of the study is to evaluate safety and tolerability of the TAK-491/CLD FDC compared to either agent alone, with particular emphasis on hypokalemia. It is expected that the combination of TAK-491 and CLD will ameliorate the hypokalemia that may be associated with CLD treatment due to renin-angiotensin aldosterone system (RAAS) blockade by the former. Six unique TAK-491/CLD FDCs will be evaluated in the proposed factorial study. The results of the TAK-491 and TAK-536 dose ranging studies indicate that doses of TAK-491 from 20 to 80 mg result in potent blood pressure reduction and good tolerability. The efficacy and safety of these TAK-491 doses are currently being validated in ongoing TAK-491 phase 3 monotherapy studies. Likewise, studies with CLD indicate that doses from 12.5 to 25 mg are associated with potent blood pressure reduction and good tolerability [9,10]. The relative blood pressure lowering potency of CLD compared to hydrochlorothiazide (HCTZ) (mg:mg) is approximately 2-fold [11,12]. Furthermore, CLD doses of 12.5 to 25 mg have been shown to reduce risk of mortality and cardiovascular morbidity in outcomes trials in hypertensive patients [7,8]. Therefore, the six TAK-491/CLD FDC dose strengths in the factorial study will be 20/12.5 mg, 20/25 mg, 40/12.5 mg, 40/25 mg, 80/12.5 mg, and 80/25 mg.

The TAK-491/CLD FDC formulation vs. TAK-491 monotherapy comparator study (TAK-491CLD_304) is designed to support the indication of initial use in patients with moderate or severe hypertension. In recognition of the observation that most hypertensive patients require combination therapy to achieve target blood pressure, the JNC-7 Report recommends consideration of initiating treatment with two drugs in patients with blood pressure greater than 20/10 mm Hg above goal [13]. The primary objective of this study is to determine if the antihypertensive effect of the FDC is greater than TAK-491 alone in patients with moderate or severe hypertension (clinic SBP 160-190 mm Hg and 24-hour mean SBP 140-170 mm Hg). Similarly, the proportion of subjects who achieve target blood pressure will be compared. In addition, general safety and tolerability will be evaluated, with particular emphasis on the incidence of hypokalemia. The results of this study are expected to establish the efficacy and safety of the TAK-491/CLD FDC as initial treatment in this higher risk population.

Preliminary Response

Question 1a

In general, a single factorial study is sufficient to establish the effectiveness of a combination product relative to the individual components if the safety and efficacy of each of the components are well characterized. The key comparison is that at the high dose of each component, the second drug adds to that effect. So for your proposed study we would consider the addition of the second component to the highest dose of the other component as the most important comparison.

We also note that there are different formulations of chlorthalidone with different bioavailability. The Thalitone formulation of chlorthalidone has substantially greater bioavailability than the Hygroton formulation. We would require some additional information to assure us that the dose of chlorthalidone used in your formulation corresponds to a more bioavailable formulation.

We are concerned that using the qualifying measurement to enroll in a study as the baseline value will predispose to an inflated estimate of the treatment effect because of regression to the mean. We suggest that either subjects qualify by cuff measurements with the ambulatory data serving as the baseline measurement or that an additional ambulatory session be conducted that would not disqualify a subject should the blood pressure for baseline not satisfy the original screening criteria.

The usual primary end point for a hypertensive study is defined by the effect at the interdosing interval. We recommend that you prespecify how the interdosing interval effect as well as peak effect will be assessed.

Question 1b

The program, if successful, would allow for the usual labeling of a combination product. We are considering what sort of safety data would be necessary and in what populations that would allow labeling as initial therapy for the treatment for hypertension.

There are issues regarding the clinical pharmacology development program that are not raised and answered in the meeting package as follows:

- The clinical trials are not conducted with the marketed dosage form of the FDC. The marketed FDC formulation is a new formulation and hence you should conduct a food interaction study using the highest strength comparing the impact of food on the exposure to the marketed FDC in subjects when fed and when fasted. The impact of food on the exposure to CLD is not known. You should define the fed/fasted state of the subjects in the pivotal clinical study.
- You propose to perform definitive bioequivalence studies with the two strengths 80/25 mg and 40/25 mg. In the absence of having information from the pivotal study, the choice of these strengths may have to be revised. There may be a need for flexible dosing with more strengths. The number of bioequivalence studies you will have to perform depends on whether the components of the different strength tablets are proportionally similar.
- The interaction potential of CLD and its pathways of disposition are not well defined. Please determine *in vitro* substrate and inhibitor status of CLD regarding CYPs and P-gp.
- TAK-491/536 is substantially metabolized, whereas for CLD the relative importance of renal to non-renal disposition is not known. The exposure to TAK-491/536 and CLD in patients with renal or hepatic impairment could change in comparison to healthy subjects. The results of the planned studies with TAK-491/536 in patients with renal or hepatic impairment are needed to assess the importance of this concern for the FDC.

Discussion during Meeting

Question 1a

Proposed study design

The sponsor proposed that the primary analysis will involve pooling of the highest dose of TAK-491 to TAK-491/placebo, and the highest dose of CLD vs. CLD/placebo. The sponsor presented a slide of the factorial design as follows:

Treatment Arms:

	Placebo	TAK-491 20 mg	TAK-491 40 mg	TAK-491 80 mg
Placebo	----	n=130	n=130	n=130
CLD 12.5 mg	n=130	n=130	n=130	n=130
CLD 25 mg	n=130	n=130	n=130	n=130

Dr. Stockbridge stated that the critical metric is to determine if the effect with the highest dose of the TAK-491/CLD combination is greater than the effect from the highest dose of either monotherapy alone.

Sample size

The sponsor was concerned that the sample size may be small for a cell-by-cell comparison. Dr. Stockbridge noted that the cell sizes are of at least the size seen in successful trials. He also noted that the sponsor was not required to have the same number of patients in each cell or to have all the cells populated. He suggested that more subjects could be shifted into the cells of interest and out of the other cells, and still maintain the overall sample size. There could also be fewer subjects in the mid-level dose groups. The sponsor could also remove the two middle doses (12.5 mg/20 mg and 12.5 mg/40 mg) and redistribute these subjects among the three corner cells of interest. The main point of this study is to show that each component of the combination contributes to the overall effect. The effect at various concentrations is also of some interest but is further supported by single entity information.

The sponsor proposed an alternative approach to pool the high dose cells of interest (80/25 and 40/25 cells). Dr. Stockbridge said that the sponsor could pool all of the active cells to show the additive effects. Ordinarily it is important to show superiority to the highest monotherapy cells because you would not generally add a second drug until maximizing the dose of the first. But there are exceptions. Dr. Temple related the Agency's experience with Ziac (bisoprolol and hydrochlorothiazide), in which the results did not show much efficacy differences in the different doses, but there were fewer side effects with the combination. Therefore, the combination was approved for initial therapy since the side effect profile was better than the individual components. The Division would be most interested in the analyses of the top right and bottom left cells.

Choice of primary endpoint

Dr. Stockbridge reiterated that using 24-hour mean blood pressure as the primary endpoint was not acceptable. The Division is most interested in a blood pressure effect at the end of the interdosing interval. The sponsor could look at the interdosing interval as the mean over the last few hours of an ambulatory record, but it was not acceptable to average the entire 24-hour interval. The sponsor responded that they plan to evaluate blood pressure at trough and peak. Their rationale for using 24-hour mean systolic blood pressure was based on numerous publications indicating that it is much better correlated with clinical outcome. In addition, among the sub-interval ABPM parameters, nocturnal blood pressure was the best predictor of cardiovascular outcomes. The sponsor proposed to measure trough blood pressure and other parameters as secondary endpoints. The Division explained that these findings were not relevant to drug effectiveness. It may be that given a choice of nocturnal control and daytime control, nocturnal looks better, but first, nocturnal control suggests a long-acting drug and second, we want overall 24-hour control to be an effect of the drug.

Dr. Stockbridge stated that the Division is concerned with drugs that show a good effect for a few hours, but then no effect at the end of the dosing interval. Measuring 24-hour mean blood pressure will not detect this, and therefore, the sponsor would need to show that the TAK-491/CLD combination has an effect at the 24-hour interdosing interval and have a good description at the peak and trough. Dr. Temple suggested that if the sponsor wins on the primary endpoint (trough pressure), then they could make the 24-hour mean blood pressure a secondary endpoint. The sponsor referred to the Carvedilol CR study design, which was approved on 24-hour mean blood pressure data. However, Dr. Stockbridge pointed out that Carvedilol CR was not a combination product and the Division knew a substantial amount about the plasma levels and response. Moreover, in that case, what was needed for approval was a demonstration that the product had the sustained blood pressure effect similar to b.i.d. dosing. Dr. Temple suggested that even if Carvedilol CR were approved using 24-hour mean blood pressure as the primary endpoint, trough measurements were also examined to be sure the effect persisted.

The sponsor explained that the FDC program design was based on feedback received from the Agency on the TAK-491 monotherapy program in which 24-hour mean blood pressure was used as the primary endpoint. Dr. Karkowsky recalled that the Division had looked at the profile before and thought that the

24-hour mean systolic blood pressure was acceptable so long as there was a substantial blood pressure effect remaining at the interdosing interval. Dr. Stockbridge stated that if the 24-hour blood pressure effect profile is flat, then a trough effect would have been demonstrated. Dr. Temple stated that the sponsor would need to show that there is an effect at trough to which the sponsor replied that there was. The sponsor defined trough as the last two hours of the dosing interval (hours 22-24).

The Agency agreed that the sponsor could do the following:

- Use 24-hour mean systolic blood pressure as the primary endpoint, but
- Measure trough at the last two hours of the dosing interval (trough levels must be consistent) and
- Show a statistically significant effect at that time.

Dr. Stockbridge made it clear that the sponsor needed to show that the combination was significantly superior to both of the monotherapies at trough. It seemed likely that if it did, 24-hour values would also show significant superiority.

The sponsor asked specifically if the trough and 24-hour mean blood pressures must be statistically significantly better for individual high dose combinations than either drug alone, or if it is acceptable for high combination cells to be pooled. Dr. Stockbridge replied that unless there was some safety advantage for the lower doses (the Ziac model), the sponsor would need to compare the top right (TAK-491/PBO) and bottom left (CLD/PBO) cells with the FDC cells. In addition, the sponsor would need to show that 80 mg TAK-491 is at the plateau of the dose-response curve.

Dose selection for chlorthalidone

The sponsor explained that although Thalitone was used for the drug interaction study conducted with TAK-491, the standard commercial formulation was used as a reference for the formulation of the FDC. The same exposure could be achieved with higher doses of the standard commercial formulation. Dr. Stockbridge stated that CLD should be at the highest dose useful in the factorial study as the combination needed to be better than the maximum dose of CLD alone. The sponsor replied that historical data showed that plasma exposure and blood pressure response are relatively flat at doses higher than 25 mg of the standard formulation.

There was discussion regarding the comparative doses of Thalitone vs. Hygroton based on their bioavailabilities. The Division stated that the sponsor needed to confirm the dose that corresponds to the maximum reasonable exposure of CLD, as it was not completely obvious that it was 25 mg. The sponsor was advised to establish the highest CLD exposure that is reasonable for monotherapy and ensure that the FDC has adequate exposure as well. The sponsor replied that they would provide a justification for using 25 mg as the highest dose.

Regression to the mean effect

To avoid a regression to the mean effect, Dr. Stockbridge advised the sponsor to use cuff measurements as screening and then use the first ABPM as the first baseline. Dr. Stockbridge added that the effect size of the regression to the mean cannot be assessed without a placebo group.

Question 1b

Labeling for initial therapy for the treatment of hypertension

Dr. Stockbridge stated that the Division has generated a document describing the analyses that are expected for approval of FDCs for initial therapy. This document, entitled "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs," could be forwarded to the sponsor after the meeting.

Food effect study requirement

The sponsor agreed to conduct a food effect study with TAK-491/CLD.

Clarification of bioavailability vs. bioequivalence studies

The sponsor clarified that they are not conducting a bioequivalence program. Clinical data will drive the efficacy and safety of the FDC formulation.

Requirement for *in vitro* substrate and inhibitor status

The sponsor agreed to conduct *in vitro* drug-drug interaction studies with TAK-491/CLD.

Requirement for hepatic/renal impairment studies

The sponsor stated that renal and hepatic impairment studies were planned with TAK-491. Dr. Hinderling agreed that this was appropriate and applicable to TAK-491/CLD.

Question 2

Does the Agency agree that the statistical methods are acceptable?

For both phase 3 studies, the primary endpoint will be 24-hour mean SBP by ambulatory blood pressure monitoring (ABPM), and secondary endpoints will include 24-hour mean diastolic blood pressure (DBP) by ABPM and clinic DBP and SBP.

For the factorial study (TAK-491CLD_302) (without the placebo-placebo cell), the primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model, with TAK-491 doses, CLD doses, region as factors and baseline as a covariate in the model. Each factor will be tested at a two-sided 0.05 significance level. If both tests for TAK-491 and CLD are statistically significant, both monotherapies will be considered to have contributed to the effect of combination treatment. Interaction between TAK-491 and CLD will be tested at a 0.05 significance level, but will not be included in the primary analysis. In addition, pairwise comparisons will be performed for each dose of TAK-491/CLD FDC against the respective TAK-491 and CLD monotherapy doses at a two-sided 0.05 significance level. Response surface and response rate analysis will also be performed.

For study TAK-491CLD_304, an ANCOVA model will be used for change from Baseline to Final Visit for 24-hour mean ABPM SBP. The model will include treatment and region as fixed effects and baseline 24-hour mean ABPM SBP as covariate. Response rate analysis will also be performed.

Preliminary Response

With ABPM, you probably can avoid having a placebo/placebo group and still address the issue of whether the second drug adds to maximum doses of the individual drugs. However, 24-hour mean blood pressure should not be the primary end point; use some measure at the interdosing interval, say, the average of the last couple of hours. Other aspects of the statistical model will need discussion in the meeting.

Discussion during Meeting

See discussion for Question 1.

Statistical considerations

Dr. Zhang stated that the overall Type 1 error should be controlled at 5%. The Division confirmed that since there is no benefit to win on one endpoint and not the other, they can both be tested at 5%. Dr. Zhang advised that ANCOVA analysis proposed by the sponsor was not relevant since the key comparison is that the highest dose combination (80/25) must beat the respective components (i.e., 80 mg TAK-491 and 25 mg HCTZ). As the Division does not typically see models with regional effects in the primary analysis model, Dr. Zhang suggested that regional differences be removed from the model.

Question 3

- a) *In response to TGRD's question at the TAK-EOP1 meeting, the Agency agreed that concurrent clinical development of the monotherapy and FDC programs was acceptable as long as the factorial study was designed after the dose-response for TAK-491 was established. TGRD would like to confirm that the Agency is willing to accept and begin reviewing the NDA for TAK-491/CLD FDC while the Agency's review of the TAK-491 monotherapy NDA is underway.*
- b) *TGRD would also like to confirm the Agency's willingness to accept the chlorthalidone co-administration study and the two long-term safety studies (a 32-week study [with a 6-week reversal phase] and a 56-week study) from the TAK-491 monotherapy program as a supportive studies for the TAK-491/CLD FDC program.*

The TAK-491/CLD FDC NDA will include the following studies: TAK-491/CLD pilot bioavailability study (TAK-491CLD_102), TAK-491/CLD pivotal bioavailability study (TAK-491CLD_103), TAK-491 and TAK-536 drug interaction and pharmacokinetic studies (described in Section 3.2), 2 pivotal phase 3 studies (TAK-491CLD_302 and TAK-491CLD_304) and 3 supportive studies from the TAK-491 monotherapy program (01-05-TL-491-006, 01-05-TL-491-009, and 01-06-TL-491-016).

Preliminary Response

Question 3a

We agree.

Question 3b

The database would likely be acceptable for labeling of the combination product as a product of convenience and for individuals not adequately controlled on the maximum dose of one of the class of drugs. To obtain initial therapy, the safety information needs to support the dosing regimens proposed, and the labeling would probably reflect population characteristics of that safety database.

Discussion during Meeting

Question 3b

The Division confirmed that the monotherapy program studies must be included as supportive. The integrated analysis will have to include all of the information. The single factorial study will be sufficient for approval of the FDC, but the longer term data and the additional data will be helpful.

CONCLUSION

Agreement was reached on the Phase 3 clinical development plan for TAK-491/CLD during this Pre-IND meeting.

POST-MEETING NOTE

Following the meeting, Quynh Nguyen of DCRP emailed a copy of the "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs" document to Ms. Deborah Yarbrough of TGRD on November 14, 2007.

Minutes preparation: Quynh Nguyen, Pharm.D.

Concurrence, Chair: *{See appended electronic signature page}*
Robert Temple, M.D.

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Takeda
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Rd:

R Temple	2/7/08
N Stockbridge	2/2/08
E Unger	2/1/08
E Fromm	2/1/08
A Karkowsky	2/1/08
A Williams	1/31/08
N Jensen	1/30/08
W Link	1/30/08
J Hung	1/29/08
J Zhang	1/29/08
P Hinderling	1/24/08

Factorial Study (TAK-491CLD_302)



Treatment Arms:

	Placebo	TAK-491 20 mg	TAK-491 40 mg	TAK-491 80 mg
Placebo	--	n=130	n=130	n=130
CLD 12.5 mg	n=130	n=130	n=130	n=130
CLD 25 mg	n=130	n=130	n=130	n=130

Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs

This document is intended to provide general guidance for use of graphs in drug labeling for initial therapy with combination antihypertensive drugs. The four graphs are to illustrate the advantage of a combination drug over its component drugs in reaching blood pressure goals of 140 and 130 mm Hg systolic and 90 and 80 mm Hg diastolic.

The graph contains regression curves for the probability of reaching a blood pressure target after treatment as a function of baseline blood pressure for the treatment groups. The curves are often based on logistic regression modeling. Some other statistical models such as probit regression may be considered. For model fitting, the following statistical considerations need attention:

1. The regression curves should fit the data reasonably well with no disproportionate leverage exerted from extreme values or potential outliers. Extensive model diagnostics are required for assessment of goodness-of-fit or a lack of fit of the fitted model. To determine overall and local fit of each regression curve, the diagnostics should include comparison of the regression curve with a LOESS non-parametric curve, comparison of the regression curve with histogram, tests (e.g., Hosmer-Lemeshow test) for fit, analysis of potential influential values. Diagnostics plots need to be generated and should include those of residuals (e.g., chi-square residual, deviance residual) versus estimated probability of achieving the blood pressure goal, difference in beta parameter value versus estimated probability, etc. If a few extreme values are suspected to cause a lack of fit, the fit may be improved by trimming these data points for further assessment. However, how many and which data points should be removed is a subjective judgment. The process of removing a few subjects for further assessment of model fit is a part of influence diagnostics. The final graphs in the drug label should include all data if possible.
2. In general, the model parameters of each treatment group should be estimated only from the data of this treatment group. In some rare situation, a simpler model such as use of a common slope for all treatment groups might improve the precision of the curves. However, applying such a simpler model to all treatment groups in regression analysis relies on strong assumptions and thus it may induce model and selection biases. Comparisons among models via statistical model selection criteria (such as AIC) need to be made, in addition to the necessary model diagnostics described above.
3. Pooling studies is discouraged because it relies on many strong and unverifiable assumptions, such as the studies pooled employ an identical design and target the same patient population, etc. When the assumptions do not hold, the curves generated from the pooled studies can be very misleading.
4. One or two studies should be chosen for display in the case that there are multiple studies conducted and pooling studies is not viable. As a general principle, the pivotal trial with the largest sample size per treatment group should be first considered. If there are multiple dose combinations, the highest dose combination is first considered with its monotherapy doses.
5. Please provide an assessment of the representation of very elderly and other fragile patients among the subjects in the factorial studies, and their adverse event profile with and tolerability to randomization to the combination.

Linked Applications

Sponsor Name

Drug Name

IND 77278

TAKEDA

TAK 491/CHLORTHALIDONE

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

/s/

ROBERT TEMPLE

02/07/2008