

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200796Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 200796

SUPPL # n/a

HFD # 110

Trade Name Edarbi

Generic Name azilsartan medoxomil

Applicant Name Takeda Pharmaceuticals North America

Approval Date, If Known

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)(1)

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.

n/a

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:

n/a

d) Did the applicant request exclusivity?

YES NO

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

Five

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?

n/a

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# n/a

n/a

NDA# n/a n/a

NDA# n/a n/a

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# n/a n/a

NDA# n/a n/a

NDA# n/a n/a

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:

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:

- 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"):

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 # 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 NO
Explain: Explain:

Investigation #2

YES

Explain:

NO

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: Alexis Childers
Title: Regulatory Health Project Manager
Date: 24 Feb 2011

Name of Office/Division Director signing form: Norman Stockbridge, M.D. Ph.D.
Title: 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/

ALEXIS T CHILDERS
02/24/2011

NORMAN L STOCKBRIDGE
02/24/2011

This certification is provided for New Drug Application (NDA 200-796, azilsartan medoxomil). 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.

Original NDA Debarment Certification

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
Dalton, Jenipher	Quality Assurance Approval	30-Mar-2010 14:57

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 200-796 BLA # n/a	NDA Supplement # n/a BLA STN # n/a	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: azilsartan medoxomil Established/Proper Name: Edarbi Dosage Form: Tablet		Applicant: Takeda Pharmaceuticals North America Agent for Applicant (if applicable): N/A
RPM: Alexis Childers		Division: Division of Cardiovascular and Renal Products
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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>Provide a brief explanation of how this product is different from the listed drug.</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 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>February 27, 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ 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 _____		<input type="checkbox"/> Received

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.

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <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>Comments:</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>	
❖ 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)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" 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 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 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 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 type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input 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 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 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>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Included
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) 25 Feb 2011 approval
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. 	Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

<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 type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" 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. 	
<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 	
<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>) 	19 Oct 2010 19 Oct 2010, 18 Feb 2011
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM N/A <input checked="" type="checkbox"/> DMEPA 4 Feb 2011 <input checked="" type="checkbox"/> DRISK 27 Jan 2011 <input checked="" type="checkbox"/> DDMAC 28 Jan 2011 <input type="checkbox"/> CSS N/A <input type="checkbox"/> Other reviews N/A
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>) 	23 Jun 2010 & 28 Feb 2011
<ul style="list-style-type: none"> ❖ 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>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" 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
<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 type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>8 Dec 2010</u> If PeRC review not necessary, explain: <u>N/A</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	See correspondence/telecons/faxes tab of action package

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

❖ Internal memoranda, telecons, etc.	See correspondence/telecons/faxes tab of action package
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• 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
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 27 Oct 2009
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 26 Apr 2007 (DCaRP) 13 Jun 2008 (CMC)
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	21 Jan 2011 Type C
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• 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 type="checkbox"/> None 25 Feb 2011
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8 Feb 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 21 Jan 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	16, Dec 2010, 3 Jan 2011, 2 Feb 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ 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>)	31 Jan 2011
❖ 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 type="checkbox"/> None 26 Oct 2010
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/25/10

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 16 Dec 2010, 3 Jan 2011
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 11 & 26 Jan 2011
❖ 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 type="checkbox"/> None 24 Feb 2011
• 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 21 Dec 2010
❖ 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 type="checkbox"/> No carc 24 Nov 2010
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 23 Sep 2010
❖ 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 type="checkbox"/> None 22 Feb 2011
• 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 16, 21 Dec 2010, 14, 19 Jan 2011
❖ Microbiology Reviews <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>)	<input checked="" type="checkbox"/> Not needed
❖ 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</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	30 Nov 2010
<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</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 9 Jun 2010 <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</i>) (<i>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 type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" 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.

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/s/

ALEXIS T CHILDERS
03/01/2011

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



US Mail address:
CDER, DCRDP (HFD-110)
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002

FDA
10903 New Hampshire Ave
Silver Spring, MD 20993-00025600

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 10903 New Hampshire Ave., Silver Spring, MD 20993-0002

Transmitted via email: dyarbrough@tgrd.com

Attention: Deborah Yarbrough

Company Name: Takeda Pharmaceuticals North America

Phone: (224) 554-2730

Subject: **NDA 200-796 21 January 2011
Meeting Minutes**

Date: 1 February 2011

Pages including this sheet: 18

From: Alexis Childers

Phone: 301-796-0442

Fax: 301-796-9838

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting Minutes

Date of meeting: 21 January 2011
Application: NDA 200-796
Drug: azilsartan medoxomil
Sponsor: Takeda Pharmaceuticals North America
Meeting Purpose: Guidance
Meeting Type: C

FDA Participants:

**Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D.	Director
Shari Targum, M.D.	Team Leader, Medical Officer
Maryann Gordon, M.D.	Medical Officer
Edward Fromm, R.Ph., RAC	Chief Regulatory Health Project Manager
Alexis Childers	Regulatory Health Project Manager
Russell Fortney, R.Ph.	Regulatory Health Project Manager

**Office of Clinical Pharmacology*

Rajanikanth Madabushi, Ph.D.	Team Leader
Divya Menon-Andersen, Ph.D.	Clinical Pharmacology Reviewer

**Office of Biostatistics, Division of Biometrics I*

John Lawrence, Ph.D.	Statistician
----------------------	--------------

Takeda Participants:

Stuart Kupfer, MD	Executive Medical Director, Clinical Science
Aziz Karim, PhD	Vice President, Clinical Pharmacology Strategy
Guoliang "Charlie" Cao, PhD	Director, Statistics
Binita Kwankin	Director, Regulatory Affairs Strategy
Deborah Yarbrough, MS, MBA	Manager, Regulatory Affairs Strategy

Background:

Azilsartan medoxomil (TAK-491) is a prodrug that rapidly converts into TAK-536 in the body. It is an angiotensin II receptor blocker (ARB). The NDA was submitted in April 2010. The PDUFA goal date is February 27, 2011. The submission proposed two doses: 40-mg and 80-mg. The Division sent initial proposed labeling with only a 40-mg dose. Based on the labeling, the sponsor requested a meeting with the Division to discuss why the 80-mg dose was removed from the proposed label.

Discussion during meeting:

The discussion focused on the reasoning for removing the 80-mg dose from the label. Dr. Stockbridge explained the Division's point of view while also indicating that a final decision has not been made. He noted that the Office Director will make the final determination on dose and approvability. Dr. Stockbridge explained that the dose-response data appeared essentially flat between 10-80 mg. There is a possible safety concern with the 80-mg dose with respect to serum creatinine, especially when co-administered with chlorthalidone. The 40-mg dose appeared to be just as effective as the 80-mg dose, with no safety concerns. Because the dose-response is small, approximately 2 mm Hg, the Division feels that patients should not be titrated from 40-mg to 80-mg. Instead, another drug should be added to boost the response.

The Sponsor explained why they chose the doses they did, and presented slides (see attached) summarizing the results from their studies. The Sponsor feels that although the dose-response is small, the drug is more efficacious and consistently lowers blood pressure at 80-mg. They also feel that the dose-response seen with their drug is similar to that seen with other ARBs.

Dr. Stockbridge emphasized that the discussion is not whether there is any difference between the dose levels; the discussion is whether or not there is enough difference to have a clinical benefit. The Sponsor suggested that if only a single dose were approved that it should be the 80-mg dose. Dr. Stockbridge suggested that the Sponsor create a memo summarizing why they feel that 80-mg is more valuable and should be approved over 40-mg.

[REDACTED] (b) (4)

The Sponsor plans to submit the memo the week of January 24, 2011.

Meeting recorder: _____
Alexis Childers

Meeting concurrence: _____
Norman Stockbridge, M.D., Ph.D.

Draft: ac 1/24/11
Final: ac 2/1/11

RD:
Fortney 1/25/11
Fromm 1/26/11
Menon-Andersen 1/26/11
Madabushi 1/26/11
Lawrence 1/31/11
Gordon 1/31/11
Targum 1/31/11
Stockbridge 1/31/11

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B4 (CCI/TS) immediately following this
page

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/s/

ALEXIS T CHILDERS
02/01/2011

NORMAN L STOCKBRIDGE
02/01/2011

Memo to file

Re: Financial disclosure review

Application Type	NDA# 200796
Submission Type; Code:	N_000, original
Medical Reviewer Established Name	Maryann Gordon, M.D. Azilsartan medoxomil
(Proposed) Trade Name	Edarbi
Therapeutic Class	Angiotensin II receptor blocker

Conclusion

I have reviewed the financial disclosures for eight of the key phase 2-3 clinical trials. There is no evidence of investigator misconduct: 1) there are numerous clinical trials conducted with this agent, 2) the studies were multicenter and international, 3) the studies were nearly all randomized and double blinded, 4) safety and efficacy results were consistent across studies and across clinical sites.

Background

The majority (>90%) of the investigators had signed the certification and or disclosure form. There was one investigator with information needing to be disclosed. This is shown below.

Attachment to Form FDA 3455 for (b) (6)

The following information is disclosed pursuant to 21 CFR § 54.4 (a)(3):

Details of (b) (6) disclosable financial arrangements and interests with regard to the Clinical Study (b) (4) are provided below:

Study (b) (6) was conducted between (b) (6).

(b) (6) has served as an expert consultant to Takeda Global Research and Development (TGRD). (b) (6) has disclosed payments from TGRD in excess of \$25,000 as reimbursement for a grant to fund ongoing research, consulting services, advisory boards and as a pharmaceutical development committee member during the study periods shown above.

Description of steps taken to minimize the potential bias of clinical study results by any of the disclosed financial interest:

(b) (6)

Based on the study design, endpoint reporting device, and the relatively small number of subjects enrolled by (b) (6), the potential for bias resulting from the disclosed payments is expected to be insignificant. The integrity and reliability of the results from (b) (6) are not compromised.

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/s/

MARYANN GORDON
01/31/2011



NDA 200796

INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Deborah O. Yarbrough, MS, MBA
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Yarbrough:

Please refer to your April 22, 2010 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAK-491 (azilsartan medoxomil) Tablets.

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 methodology as shown below is acceptable:

Apparatus: 2 (Paddle) x 50 rpm
Medium: (b) (4) USP Phosphate Buffer (pH 7.8) 900 mL at 37°C
Sampling time: 10, 15, 20, 30, and 45 minutes

However, azilsartan medoxomil immediately release tablets dissolved rapidly using the above dissolution method, i.e., (b) (4), therefore, the specifications should be revised as follows:

Specifications: From Q= (b) (4)
To Q= (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
12/21/2010



NDA 200796

INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Deborah O. Yarbrough, MS, MBA
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Yarbrough:

Please refer to your April 22, 2010 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAK-491 (azilsartan medoxomil) Tablets.

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.

- The P3 section does not include values for some process parameters. [REDACTED] (b) (4) [REDACTED]. Note that a complete description of the commercial scale drug product manufacturing process is required and should include all process parameters. Therefore, include a master production record /or a detailed manufacturing process description in section P.3.3 (drug product) of the application, in accordance with 21CFR 314.50 d(1)(ii)(c). The Agency recognizes that changes to process parameters that are not critical (e.g. statistically non significant parameters) can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.

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
12/17/2010



NDA 200796

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Takeda Pharmaceuticals North America
One Takeda Parkway
Deerfield, Illinois 60015

ATTENTION: Deborah O. Yarbrough, M.S., MBA
Manager, Regulatory Strategy

Dear Ms. Yarbrough:

Please refer to your New Drug Application (NDA) dated April 22, 2010, received April 27, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azilsartan Medoxomil Tablets, 40 mg and 80 mg.

We also refer to your August 13, 2010, correspondence, received August 13, 2010, requesting review of your proposed proprietary name, Edarbi. We have completed our review of the proposed proprietary name, Edarbi and have concluded that it is acceptable.

The proposed proprietary name, Edarbi, 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 August 13, 2010, 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, Alexis Childers, at 301-796-0442.

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
10/19/2010



NDA 200796

INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Deborah O. Yarbrough, MS, MBA
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Yarbrough:

Please refer to your April 22, 2010 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAK-491 (azilsartan medoxomil) Tablets.

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.

- For your dissolution method using a paddle x 50 rpm, you investigated pH range for the medium, (b) (4), and finally proposed the pH of 7.8. However, you did not provide justification for a pH medium 7.8 (b) (4) (Table 5, p. 11 out of 28). Provide further justification to support using pH 7.8 medium (b) (4). Otherwise, it is recommended that a paddle x 50 rpm (b) (4) be employed.

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
10/04/2010



NDA 200796

INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Deborah O. Yarbrough, MS, MBA
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Yarbrough:

Please refer to your April 22, 2010 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAK-491 (azilsartan medoxomil) Tablets.

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.

(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
09/30/2010

Executive CAC

Date of Meeting: September 14, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Barbara Hill, Ph.D., DDDP, Alternate Member
Muriel Saulnier, D.V.M, Ph.D., D.A.B.T., DCaRP Team Leader
Philip Gatti, Ph.D., DCaRP Presenting Reviewer

Author of Draft: Philip Gatti, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 200-796

Drug Name: azilsartan

Sponsor: Takeda

Four carcinogenicity studies were reviewed. Two (rat and Tg.rasH2 mouse) for the pro drug, TAK 491, and two (rat and Tg.rasH2 mouse) for the metabolite, TAK 563-MII.

Pro Drug TAK 491:

Rat Carcinogenicity Study

Strain: F344/Jcl rats

Dose (oral): 60, 200 and 600 mg/kg/day

Vehicle: 0.5w/v% methylcellulose in 0.005w/v% citric acid

Duration: 24 months

The incidence of hemolymphoreticular histiocytic sarcomas in rats was numerically increased at the high dose in the females as shown in the following table.

	Control (Combined)	60 mg/kg	200 mg/kg	600 mg/kg
Incidence	1/100	1/50	1/50	4/50
Poly-3 adjusted incidence rate	1.1%	2.2%	2.1%	8.2%
p-value of pairwise and trend tests	.0168 (trend)	.5604	.5730	.0483

The two control groups received the same vehicle treatment. Relevant historical data were not available. Therefore the concurrent control data from this study and the study with the metabolite (discussed below) were used to determine whether this tumor was

common. In addition to the tumor diagnosed in the one female control, these tumors were also diagnosed in 2/100 males in vehicle control groups and in 1/50 females in a vehicle control group in the study of the metabolite. In the absence of historical control data, the concurrent control data suggest that these tumors should be assessed using common tumor criteria of $\alpha=0.005$ for trend and $\alpha=0.01$ for pairwise comparisons. Consequently, the trend and pairwise analyses do not reach statistical significance. In addition to the statistical analysis, the mode of action of the compound, i.e. competitive reversible antagonist at AT-1 receptors, does not suggest that these tumors are pharmacologically related.

Tg.rasH2 Mouse Carcinogenicity Study

Doses (oral): 50, 150 and 450 mg/kg/day

Vehicle: 0.5w/v% methylcellulose in 0.005w/v% citric acid

Duration: 26 weeks

No neoplasm was statistically significant by the CDER criteria.

Metabolite TAK 536-MII:

Rat Carcinogenicity Study

Strain: F344/Jcl rats

Dose (oral): 100 (males), 300 (both sexes), 1000 (both sexes) and 3000 (females)

Vehicle: Corn oil

Duration 24 months

No neoplasm was statistically significant by the CDER criteria.

Tg.rasH2 Mouse Carcinogenicity Study

Concentration in diet: 1.25, 3.5 and 5%

Controls: Normal diet

Duration: 26 weeks

No neoplasm was statistically significant by the CDER criteria.

Executive CAC Recommendations and Conclusions:

Pro Drug TAK-491

Rat:

- The Committee agreed that the study was acceptable, noting prior FDA concurrence with the protocol.
- The Committee concurred that there no drug-related neoplasms.

Tg.rasH2 Mouse:

- The Committee agreed that the study was acceptable, noting prior FDA concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms

Metabolite TAK-536 MII:

Rat:

- The Committee agreed that the study was acceptable, noting prior FDA concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Tg.rasH2 Mouse:

- The Committee agreed that the study was acceptable, noting prior FDA concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DCRP
/MSaulnier, DCRP
/PGatti, DCRP
/AChilders, DCRP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
09/23/2010

DAVID JACOBSON KRAM
09/23/2010



NDA 200796

INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Deborah O. Yarbrough, MS, MBA
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Yarbrough:

Please refer to your April 22, 2010 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAK-491 (azilsartan medoxomil) Tablets.

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.

Drug Substance

1. Concerning Comparability protocol TAK-491-14510, the data requirements in your proposal appear to be adequate [REDACTED] ^{(b) (4)}, however, we recommend submitting a Supplement - Changes Being Effected in 30 days, containing all the data necessary to support this change. Revise your protocol accordingly.
2. Clarify which of the two proposed methods (HPLC or UPLC) for the identification, related substances and assay is the primary regulatory method. The other method may be considered the alternative method.
3. The FDA recommends using an RSD of at least 5 injections of the standard preparation [REDACTED] ^{(b) (4)} [REDACTED] in the system suitability evaluation for the HPLC method for related substances. Revise your method accordingly.

Drug Product

4. P.2.1.2 Excipients

Justify your selection of the particular grade of hydroxypropyl cellulose in terms of its molecular weight and particle size; since its (b) (4) depend on these attributes?

5. P.2.2. Pharmaceutical Development

Design of Experiments;

(b) (4)

6. P.2.3 Manufacturing Process Development

(b) (4)

7. P.3.4 Controls of Critical Steps and Intermediates

- i. Clarify the absence of an in-process periodic control check for tablet hardness in your executed batch record (3.2.R.1).
- ii. Clarify the discrepancy between the ranges for the following key process operating parameters presented in P.3.4 and the executed batch records for the 20 mg tablet (Document No. ZMr-624-905):

(b) (4)

8. P.5.1 Specification(s)

- i. Include the shape of the tablet in the 'Appearance' test (b) (4).
- ii. State which analytical method will be used for routine batch release, HPLC or UPLC, for related substances, content uniformity and assay. Clearly denote the regulatory and alternate methods in the specification.
- iii. Since you have not provided any scientific evidence for demonstrating the growth inhibitory properties of the drug product as stated in ICH Q6A Decision Tree #8, include the microbial limit testing in the specification of the drug product. We are cognizant of your reasons provided in P.2.5 for excluding this test.

9. P.8.1 Stability Summary and Conclusion

Based on the provided 12 months stability data at 25°C/60% RH and 6 months at 40°C/75% RH and the statistical treatment of the data ((b) (4)) reduce the acceptance criterion of the (b) (4) degradate and concomitantly that for Total Degradates

10. Review of Common Technical Document-Quality (Ctd-Q) Module

1A. Labeling & Package Insert:

- i. The established name on the container label should be in parenthesis, with the word 'tablets' inserted after the parenthesis.
- ii. The font size and prominence of the word "tablet" should be increased in the bottle label.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

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/s/

RAMESH K SOOD
09/03/2010



NDA 200796

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Takeda Pharmaceuticals North America
675 North Field Drive
Lake Forest, IL 60045

ATTENTION: Binita Kwankin
Director, Regulatory Strategy

Dear Ms. Kwankin:

Please refer to your New Drug Application (NDA) dated April 22, 2010, received April 27, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azilsartan Medoxomil Tablets, 40 mg and 80 mg.

We also refer to your May 11, 2010, correspondence, received May 12, 2010, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable (b) (4).

(b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

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, Alexis Childers at 301-796-0442.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

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/s/

CAROL A HOLQUIST
08/06/2010



NDA 200-796

FILING COMMUNICATION

Takeda Pharmaceuticals North America
Attention: Binita Kwankin
Director, Regulatory Strategy
675 N. Field Drive
Lake Forest, IL 60045

Dear Ms. Kwankin:

Please refer to your new drug application (NDA) dated 22 April 2010, received 27 April 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (azilsartan medoxomil) 40 and 80 mg tablets.

We also refer to your submission dated May 11, 2010 containing a proprietary name request.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is **February 27, 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, mid-cycle, 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 requirement/commitment requests by **January 16, 2011**.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have also completed a preliminary review of your proposed label and have a few comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. Please submit the following formatting changes to the label:

1. Per 21 CFR 201.57(a)(4), the boxed warning in the highlight section should be bolded and bulleted.
2. Add a warning to the Full Prescribing Information Contents section, prior to section 1. The text should read, "**WARNING: AVOID USE IN PREGNANCY**".

3. When stating a trade name, please only capitalize the first letter. This applies to the trade name everywhere in the label, with the exception of the title in the highlights section.
4. In Section 2, Dosage and Administration please include the route of administration.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. We also acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral and waiver requests are denied.

If you have any questions, please call Alexis Childers, Regulatory Project Manager, at (301) 796-0442.

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
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

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/s/

NORMAN L STOCKBRIDGE
07/07/2010

REQUEST FOR CONSULTATION

TO (Office/Division): Raanan Bloom, OPS/PARS, (301)796-2185

FROM (Name, Office/Division, and Phone Number of Requestor):
Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of Kasturi Srinivasachar/Prafull Shiromani

DATE
July 6, 2010

IND NO.

NDA NO.
200796

TYPE OF DOCUMENT
original submission

DATE OF DOCUMENT
April 28, 2010

NAME OF DRUG
Azilsartan medoxomil
tablets

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
cardio-renal

DESIRED COMPLETION DATE
November 27, 2010

NAME OF FIRM: Takeda Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The applicant claims categorical exclusion from preparation of an environmental assessment. A review of the rationale (calculation) in their comprehensive report is requested. This is an electronic submission

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

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/s/

DON L HENRY
07/06/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 200-796 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Azilsartan Medoxomil (TAK-491) Established/Proper Name: (b) (4) Dosage Form: Tablet Strengths: 40mg, 80mg		
Applicant: Takeda Pharmaceuticals North America Agent for Applicant (if applicable): N/A		
Date of Application: April 22, 2010 Date of Receipt: April 27, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: February 27, 2011	Action Goal Date (if different): N/A	
Filing Date: June 26, 2010	Date of Filing Meeting: June 8, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Azilsartan medoxomil is an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): IND 71,867 (b)(4)				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.			X	
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X																	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X																	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X																	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:			X																	
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X																	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>		X		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			Consult to PHMS to determine how pediatrics should be addressed. Meet with PeRC 6 weeks before action date.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			Waive premature & newborns up to 28 days and infants >28days to < 12 months Defer 12 months to <17 years
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> Carcinogenicity stats consult 5/24/10	X			QT consulted under IND (review dated 11/13/09)

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): April 26, 2007 <i>If yes, distribute minutes before filing meeting</i>	X			Minutes dated June 4, 2007
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): October 27, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			Minutes dated December 10, 2009
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>			X	

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8 June 2010

BLA/NDA/Supp #: NDA 200-796

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Azilsartan Medoxomil (TAK-491)

DOSAGE FORM/STRENGTH: 40 & 80 mg

APPLICANT: Takeda

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Hypertension

BACKGROUND:

Azilsartain medoxomil (TAK-491) is a prodrug that converts into TAK 536 once metabolized and acts as an angiotensin II receptor blocker. With this NDA, the sponsor would like to obtain the regular antihypertensive indication (b) (4). They have performed studies to (b) (4) to Valsartan and olmesartan and performed co-administration studies with chlorthalidone (CLD) and amlodapine.

There were four milestone meetings between the sponsor and the FDA: EOP1 April 2006, EOP2 April 2007, Type C May 2009, and the pre-NDA December 2009. It was determined at the pre-NDA meeting in December 2009 that this NDA submission for TAK-491 would include all of the data for TAK -491, some data from TAK-536, and some supportive data for the co-administration with chlorthalidone. (The INDs associated with this NDA are IND 71,867 (b) (4).)

The Phase 3 program main objectives were to compare the efficacy, safety and tolerability of TAK-491 with placebo and two other angiotensin II receptor blockers (ARB), olmesartan medoxomil and valsartan. Another objective was to characterize the antihypertensive effects of TAK-491 during long term administration, in subpopulations and when co administered with other antihypertensive agents. There were 5 randomized, controlled, monotherapy studies of 6 weeks or 6 months duration, 2 randomized, controlled, 6 week studies where TAK-491 was co administered with CLD 25 mg and with amlodipine 5 mg, and 2 open label studies up to 56 weeks in length. The proposed starting dose is 40 mg but may be increased to 80 mg alone or in combination with other antihypertensive agents.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alexis Childers	X
	CPMS/TL:	Ed Fromm	X
Cross-Discipline Team Leader (CDTL)	Stephen Grant		N
Clinical	Reviewer:	Maryann Gordon	Y
	TL:	N/A	
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Divya Menon-Anderson	Y
	TL:	Raj Madabushi	N
Biostatistics	Reviewer:	John Lawrence	N
	TL:	Hsien Ming Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Philip Gatti	Y
	TL:	Patricia Harlow	Y
Statistics (carcinogenicity)	Reviewer:	Mathew Jackson	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Prafull Shiromani (drug	Y

		product); Charles Jewell (drug substance); Albert Chen (Biopharm)	Y N
	TL:	Kasturi Srinivasachar; Angelica Dorantes (Biopharm)	Y N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	N
	TL:	N/A	
OSE/DRISK (REMS)	Reviewer:	Barbara Fuller	Y
	TL:	Claudia Karwoski	N
Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	Y
	TL:	Tejashri Purohit-Sheth	N
Other reviewers	N/A		
Other attendees	Robert Temple, Mary Dempsey, Aliza Thompson, Abraham Karkowsky, Ginneh Stowe, Alison Blaus, Mary Ross Southworth, Norman Stockbridge, Nina Ton		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: There are a lot of studies, targeting the main studies to review. Maryann will do the review in conjunction with John Lawrence.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: Since large number of studies with a large number of subjects that are very consistent in their outcome.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments: This NME is not first in its class. Norman Stockbridge to send a note to John Jenkins with his rationale.</p> <p>If no, for an original NME or BLA application, include the reason. For example:</p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></p>	
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: 67 studies. There will be a scoping meeting scheduled to determine which to review</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: per email after meeting John Lawrence noted the application was fileable.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: 7 carcinogenicity studies. 2 have been reviewed. Stats consult has been requested. E-CAC scheduled for 9/14/10</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>PRODUCT QUALITY (CMC)</p> <p>Comments: BioPharm needs to review as well but were not present at the meeting.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: Requested a consult report to EA officer.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: both abroad and domestic sites. Request made but not scheduled yet</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CMC Labeling Review (BLAs/BLA supplements only)</p> <p>Comments: N/A</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
---	---

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Robert Temple	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

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/s/

ALEXIS T CHILDERS
06/23/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Alexis Childers, RHPM, ODE I/ DCRP, 301-796-0442

REQUEST DATE
May 24, 2010

IND NO.
71,867

NDA/BLA NO.
200,796

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG

Azilsartan Medoxomil

PRIORITY CONSIDERATION

Standard

CLASSIFICATION OF DRUG

NME

DESIRED COMPLETION DATE

(Generally 1 week before the wrap-up meeting)

December 22, 2010

NAME OF FIRM:

Takeda

PDUFA Date: February 27, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

PACKAGE INSERT (PI)

PATIENT PACKAGE INSERT (PPI)

CARTON/CONTAINER LABELING

MEDICATION GUIDE

INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

ORIGINAL NDA/BLA

IND

EFFICACY SUPPLEMENT

SAFETY SUPPLEMENT

LABELING SUPPLEMENT

PLR CONVERSION

REASON FOR LABELING CONSULT

INITIAL PROPOSED LABELING

LABELING REVISION

EDR link to submission:

EDR : <\\CDSESUB1\EVSPROD\NDA200796\200796.ENX>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: September 27, 2010

Labeling Meetings: TBD

Wrap-Up Meeting: TBD for first week of January, 2011

SIGNATURE OF REQUESTER

Alexis Childers

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

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/s/

ALEXIS T CHILDERS
05/24/2010

REQUEST FOR CONSULTATION

TO (Office/Division): Karl Lin, Team Leader, Division of Biometrics 6 (Applications in Pharmacology / Toxicology)

FROM (Name, Office/Division, and Phone Number of Requestor): Alexis Childers, ODE 1/DCaRP, (301)796-0442

DATE
20 May 2010

IND NO.
71867, (b) (4)

NDA NO.
200-796

TYPE OF DOCUMENT
NDA Submission

DATE OF DOCUMENT
22 April 2010

NAME OF DRUG
azilsartan medoxomil

PRIORITY CONSIDERATION
standard NDA

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
9 August 2010

NAME OF FIRM: Takeda

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|---|
| <input type="checkbox"/> CLINICAL | <input checked="" type="checkbox"/> NONCLINICAL |
|-----------------------------------|---|

COMMENTS / SPECIAL INSTRUCTIONS:

We are requesting your assistance in the review of the carcinogenicity data for azilsartan. This submission is located at the following link: \\CDSESUB1\EVSPROD\NDA200796\200796.ENX

There studies to review are as follows:

- 1) TAK-491-10808: 24 month rat carci study with prodrug (TAK-491)
- 2) TAK-491-10809-001A: 26 week ras-mouse carci study with prodrug (TAK-491)
- 3) TAK-536-10008: 24 month rat carci study with metabolite (TAK-536 MII)
- 4) TAK-536-10010: 26 week ras mouse carci study with metabolite (TAK-536 MII)
- 5) TAK-536-10009: 24 month rat carci study with additional dose in females of the metabolite (TAK-536 MII).

The data regarding carcinogenicity arrived in the submission dated 28 April 2010 (module 4. The Pharmacology/ Toxicology reviewer for this NDA is Philip Gatti (301-796-2088). Once a statistician has been assigned, please let myself and Philip know that person. This data will need to be taken in front of the Exec CAC in September, so we

are hoping to have your review by August 9 (or sooner) since we will need it to finalize our reviews. If you have any questions, please do not hesitate to contact Phil or me. Thank you in advance! Alexis

SIGNATURE OF REQUESTOR

Alexis Childers

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

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/s/

ALEXIS T CHILDERS
05/24/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	TAK-491

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/s/

ALEXIS T CHILDERS
05/05/2010



NDA 200796

NDA ACKNOWLEDGMENT

Takeda Global Research & Development Center, Inc.
Attention: Deborah O. Yarbrough, MS, MBA
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Yarbrough:

We have received your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: TAK-491 (azilsartan medoxomil) Tablets, 40 and 80 mg

Date of Application: April 22, 2010

Date of Receipt: April 27, 2010

Our Reference Number: NDA 200796

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 June 26, 2010 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.

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:

Ms. Alexis Childers
Regulatory Health Project Manager
(301) 796-0442

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200796

ORIG-1

TAKEDA GLOBAL
RESEARCH
DEVELOPMENT
CENTER INC

TAK-491

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/s/

EDWARD J FROMM
05/04/2010



April 22, 2010

Mr. Scott J. MacIntire
District Director, HFR-CE600
Chicago District Office (CHI-DO)
550 W. Jackson Boulevard., Suite 1500, South
Chicago, IL 60661

**Re: NDA 200,796: Original NDA
TAK-491 (azilsartan medoxomil) tablets**

Dear Mr. MacIntire:

Please be advised that Takeda Global Research & Development Center, Inc. (TGRD) will be submitting a New Drug Application (NDA 200,796) for TAK-491 (azilsartan medoxomil) tablets in electronic common Technical Document (eCTD) format to the Food and Drug Administration Center for Drug Evaluation and Research on or before April 30, 2010.

Pursuant to Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" June 2008, Section "K", TGRD will not be submitting a paper copy of the NDA to the Chicago District Office. If you require any section for review, please contact Quynh Nguyen, FDA Project Manager, in the Division of Cardiovascular and Renal Products at (301)796-0510.

This notification to the FDA Chicago District Office serves to fulfill the requirements under 21 CFR §314.50(l)(3) for the above referenced electronic application.

Please do not hesitate to contact me if you have any additional questions.

Sincerely,

Deborah O. Yarbrough, MS, MBA
Manager, Regulatory Affairs
Takeda Global Research & Development Center, Inc.
Main Line: (224) 554-6500
Phone: (847) 582-3511
Facsimile: (224) 554-7870
Email: dyarbrough@tgrd.com

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

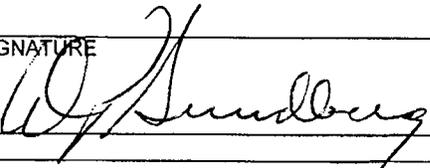
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Investigator list included in 1.3.4	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Dean Sundberg	TITLE Senior Vice President, Regulatory Affairs
FIRM/ORGANIZATION Takeda Global Research and Development Center, Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) 03/30/2010

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

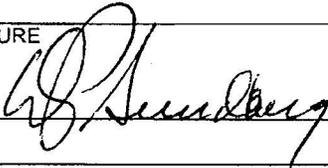
TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6), who participated
Name of clinical investigator
as a clinical investigator in the submitted study (b) (6)
Name of
clinical study is submitted in accordance with 21 CFR part 54. The
named individual has participated in financial arrangements or holds financial interests that are
required to be disclosed as follows:

Please mark the applicable check boxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Dean Sundberg	TITLE Senior Vice President, Regulatory Affairs
FIRM/ORGANIZATION Takeda Global Research and Development Center, Inc.	
SIGNATURE 	Date (mm/dd/yyyy) 03/30/2010

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

Attachment to Form FDA 3455 for [REDACTED] (b) (6)

The following information is disclosed pursuant to 21 CFR § 54.4 (a)(3):

Details of [REDACTED] (b) (6) **disclosable financial arrangements and interests with regard to the Clinical Study** [REDACTED] (b) (6) **are provided below:**

[REDACTED] (b) (6) was conducted between [REDACTED] (b) (6).

[REDACTED] (b) (6) has served as an expert consultant to Takeda Global Research and Development (TGRD). [REDACTED] (b) (6) has disclosed payments from TGRD in excess of \$25,000 as reimbursement for a grant to fund ongoing research, consulting services, advisory boards and as a pharmaceutical development committee member during the study periods shown above.

Description of steps taken to minimize the potential bias of clinical study results by any of the disclosed financial interest:

[REDACTED] (b) (6)

Based on the study design, endpoint reporting device, and the relatively small number of subjects enrolled by [REDACTED] (b) (6), the potential for bias resulting from the disclosed payments is expected to be insignificant. The integrity and reliability of the results from [REDACTED] (b) (6) are not compromised.

**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: dyarbrough@tgrd.com

Attention: Ms. Deborah Yarbrough

Sponsor: Takeda Global Research & Development Center, Inc.

Phone: (847) 582-3511

Subject: **Pre-NDA Meeting Minutes**

Date: December 10, 2009

Pages including this sheet: 64

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.

Pre-NDA Meeting with Sponsor

Application Number: IND 71,867
Sponsor: Takeda Global Research and Development Center, Inc.
Drug: TAK-491 (azilsartan medoxomil)
Type of Meeting: Pre-NDA
Classification: B
Meeting Date: October 27, 2009
Briefing Package Received: September 25, 2009
Confirmation Date: September 2, 2009
Meeting Request Received: August 13, 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. Clinical Reviewer
Charles Resnick, Ph.D. Pharmacology Team Leader
Albert DeFelice, Ph.D. Pharmacology Team Leader
Philip Gatti, Ph.D. Pharmacologist
Edward Fromm, R.Ph., RAC Chief, Project Management Staff
Quynh Nguyen, Pharm.D., RAC Regulatory Health Project Manager

Office of Biostatistics, Division of Biometrics I

Valeria Freidlin, Ph.D. Statistician

Office Clinical Pharmacology, Division of Clinical Pharmacology I

Divya Menon-Andersen, Ph.D. Clinical Pharmacology Reviewer

Office of Compliance, Division of Scientific Investigations

Tejashri Purohit-Sheth, M.D. Branch Chief, Good Clinical Practice Branch II

Takeda Global Research and Development Center, Inc. (TGRD)

Karen Asin, Ph.D. Director, Pharmacology
Bruce Barger, D.O. Associate Medical Director, Pharmacovigilance
Guoliang "Charlie" Cao, Ph.D. Associate Director, Biometrics and Data Management
Rosemarie Green, R.Ph. Asst. Proj. Director, Strategic Project Management
Aziz Karim, Ph.D. Vice President Clinical Pharmacology Strategy
Stuart Kupfer, M.D. Executive Medical Director, Clinical Science

Binita Kwankin
Neila Smith, M.D.
Deborah Yarbrough, M.S., M.B.A.
Jeff Zhang
(b) (4)
Fiona Mortimer Ph.D.

Director, Regulatory Affairs Strategy
Senior Medical Director, Pharmacovigilance
Manager, Regulatory Affairs Strategy
Principal Statistician, Biometrics and Data Management
(b) (4)
Associate Director, EU Regulatory Affairs

BACKGROUND

TAK-491 (azilsartan medoxomil) is being developed by Takeda Research & Development Center, Inc. for the treatment of hypertension. TAK-491 is a prodrug that is rapidly and completely converted to TAK-536, a highly potent, long-acting angiotensin II receptor blocker (ARB). The sponsor requested this meeting to discuss their plans for submission of a New Drug Application (NDA) anticipated in April 2010. The Division's Preliminary Responses were sent to the sponsor on October 23, 2009. The sponsor requested further discussion of Questions 6, 7, 11, 14, 25 and the Additional Preliminary Responses as noted below.

DISCUSSION

NDA Administrative Questions

1. Does FDA agree with TGRD's plan for financial disclosure information in the NDA?

Preliminary Response

We agree.

2. Does FDA have any comments on TGRD's proposed pediatric plan to meet PREA requirements?

Preliminary Response

The proposed pediatric plan will need to be reviewed by the Pediatric Review Committee (PeRC).

3. Does FDA agree with TGRD's plan to submit only the text portion of clinical study reports for studies considered supportive?

Preliminary Response

As listed in the briefing book, the dose – response study conducted using the capsule formulation of TAK 491 (study # 491-005) appears to be a supportive study. Please submit the complete study report (summary, detailed report, relevant SAS datasets) for study 491-005. Text portions may be submitted for the other clinical pharmacology studies that are considered to be supportive. If additional information about the supportive trials is needed by the reviewer of the NDA, you would be expected to supply it in a timely manner.

4. Does the FDA agree with the approach of providing CIOMS for deaths and other SAEs and PANs for adverse events leading to discontinuation?

Preliminary Response

Yes. Also, copies of the CRFs for these subjects would need to be submitted.

5. Does FDA agree with TGRD's proposal to submit SAS datasets and not patient profiles in the filing?

Preliminary Response

We agree.

6. Does FDA agree with TGRD's proposal for submission of SAS XPORT transport files and with the request for test transfers of datasets to ensure compliance with FDA requirements?

Preliminary Response

We agree, but please note that regardless of CDISC SDTM standards, we require you to submit the investigator original (before any data clarification or query process) and final (used for coding) entries for verbatim adverse event terms. If the data clarification or query process changed any other CRF fields frequently (e.g., dates), we would like the original and final versions of those fields as well.

Discussion during Meeting

The sponsor presented their submission proposal (see attached slide 1). The sponsor stated that the databases would include only the final term and not the original term before query and the listings would be generated from the audit trail from studies that use e-CRF for all Phase 3 studies only (the Phase 2 studies had paper data collection). The listings proposed would include subject identifier, visit number, AE verbatim term (original entry, final entry) and reason for change (e.g., entry error) and these listings would be in pdf format. However, Dr. Marciniak requested that SAS datasets be submitted since pdf files could not be automatically checked. Dr. Stockbridge added that the dataset would need to be "machine-readable" so that the reviewer could link the AE in the dataset to the AE in the final submission listing. The Division agreed that the SAS dataset did not have to be in SDTM. The sponsor was encouraged to submit mock-ups for review.

The sponsor agreed that the Division's Preliminary Response regarding frequently changed CRF fields would be addressed in the NDA. The sponsor will also follow up with the EDR staff regarding dataset test transfers.

7. Does FDA agree with TGRD's proposal for submission of phase 1 datasets?

Preliminary Response

No. Please submit the complete study report (summary, detailed report, relevant SAS datasets) for all primary Phase 1 clinical pharmacology studies.

Discussion during Meeting

The sponsor presented their submission proposal as follows (see slide 2):

- Submit study reports for all primary Phase I studies
- Submit SAS datasets for all primary Phase I studies except TAK-536-GHBA-328
 - Demography, AE, Laboratory results, vital signs, dose administration, ECG (when applicable), PK/PD
 - as SAS transport file
 - A description of each data in a Define.pdf file
 - In Takeda standard, not in SDTM format
- A PD study TAK-536-GHBA-328 was completed before ICH E3.
 - submit study report, not SAS dataset.

The Division agreed with the sponsor's proposal and also requested that annotated case report forms be submitted. The sponsor proposed to submit only the study report and not the SAS dataset

for the PD study, TAK-536-GHBA-328, because the format of the dataset was still being assessed as the study was completed before the ICH E3 Guidance issued. Dr. Menon-Andersen stated that the dataset for this study is required because it is a key bridging study. The Division agreed that the dataset for the PD study, TAK-536-GHBA-328 PD, would not have to be in the same format as the other primary Phase 1 studies since it was completed in the mid-1990s.

8. Does FDA agree with TGRD's proposed analysis dataset approach for TAK-491 phase 2 and 3 studies?

Preliminary Response

We agree.

9. Does the FDA agree with the ISS and ISE data set approach?

Preliminary Response

We agree.

10. Does FDA agree that the planned define.xml construction and no-limit file size of the transport files are acceptable?

Preliminary Response

We agree.

Nonclinical Questions

11. Does FDA agree that the genotoxicity data presented herein support TGRD's conclusion that the positive results seen with TAK-491, its metabolites, and (b) (4) impurity in certain in vitro genotoxicity assays do not constitute a hazard to humans?

Preliminary Response

No. Based on the observation that very little of the MII metabolite is formed in the mouse, we would like to see the results of a mouse micronucleus test using the MII metabolite.

Discussion during Meeting

The sponsor stated that exposures to the M-II metabolite in the TAK-491 *in vivo* mouse micronucleus test resulted in C_{max} and AUC margins of 8.57x and 0.93x, respectively, relative to geometric mean exposures in human volunteers dosed with TAK-491 at 80 mg. Dr. Resnick pointed out that not much of a margin is seen with AUC values and the Division would like to see doses pushed to the maximum tolerated level. The sponsor responded that C_{max}, rather than AUC, is the more important parameter for genotoxicity studies *in vivo*.

In addition, the sponsor noted that carcinogenicity studies have been completed with the TAK-536 M-II metabolite in rats and mice (see slide 8) and preliminary data from these studies indicate that TAK-536 M-II is not oncogenic. The sponsor asserted that results from these carcinogenicity studies should be considered definitive relative to the results of the genotoxicity test panel. The sponsor will include the final reports in the NDA.

Post-Meeting Note: In a November 2, 2009 email correspondence from Ms. Quynh Nguyen of DCRP to Ms. Deborah Yarbrough of TGRD, the Division rescinded its request for the mouse micronucleus study using the TAK-536 M-II metabolite.

12. Does FDA agree with TGRD's plan to present the TAK-491 and TAK-536 nonclinical data in the NDA?

Preliminary Response

Yes.

13. Does FDA agree with the strategy for inclusion of only the TAK-491 and TAK-536 monotherapy (and not the TAK-491CLD, TAK-491CCB, and TAK-536/pioglitazone) nonclinical study reports in the nonclinical sections of the TAK-491 monotherapy CTD?

Preliminary Response

No. We would like to see summaries of the data for the combination studies with TAK-491/chlorthalidone, TAK-491/amlodipine and TAK-536/pioglitazone in order to assess any potential drug interactions.

14. Does FDA agree that TGRD's nonclinical development plan for TAK-491 supports filing of the TAK-491 NDA for the proposed indication?

Preliminary Response

No. In addition to the mouse micronucleus test with the metabolite, we recommend performing a seg III reproductive toxicity study in rats with the MII metabolite and a 9-month general toxicity study in dogs with the MII metabolite.

Discussion during Meeting

Dr. Resnick stated that the 9-month toxicity study in dogs is needed to characterize the general toxicity of the TAK-536 M-II metabolite. Although the minutes of the April 6, 2006 End-of-Phase 1 meeting indicate that the 13-week rat and dog studies may be sufficient pending a review of the data, Dr. Resnick stated that the rationale for this position was unclear given the chronic administration of the parent molecule. The sponsor replied that the studies completed to date are consistent with the 2008 Guidance for Industry on Safety Testing of Drug Metabolites. Dr. Resnick agreed to review that guidance and reconsider the need for the 9-month dog study.

Dr. Resnick noted that previous meeting minutes indicate poor bioavailability for the M-II metabolite in the tested animal species.. The sponsor responded that adequate exposures and margins had been achieved when the M-II metabolite was administered orally and presented data from the 13-week rat and dog studies (see slides 14-16). The sponsor also noted that a chronic toxicity evaluation of the TAK-536 M-II metabolite had been conducted in at least one species, the rat, referring to the evaluation for carcinogenic potential. Dr. Resnick questioned whether the carcinogenicity study protocols were adequate to evaluate toxicities other than neoplasia. The sponsor agreed to resubmit the protocols for those studies.

Regarding the need for a Seg III study to complete the DART program for the TAK-536 M-II metabolite, the sponsor argued that this study was unnecessary as they are conducting a 13-week juvenile rat study with TAK-491 plus TAK-536 M-II, they have conducted Seg II studies in rats and rabbits with TAK-536 M-II and, furthermore, the parent drug is an angiotensin II AT1 receptor antagonist and, as such, is already expected to receive restrictive pregnancy labeling (black box warning against use during 2nd and 3rd trimesters).

FDA agreed that the data from the juvenile toxicity studies could be submitted as part of the 4- month NDA safety update.

Post-Meeting Note: In a November 2, 2009 email correspondence from Ms. Quynh Nguyen of DCRP to Ms. Deborah Yarbrough of TGRD, the Division rescinded its request to perform a 9-month general toxicity study in dogs and a seg III reproductive toxicity study in rats using the TAK-536 M-II metabolite.

Clinical Questions

15. Does FDA agree with TGRD's proposed strategy to include TAK-536 pharmacokinetic and pharmacodynamic data in the TAK-491 package insert?

Preliminary Response

We agree with the proposed strategy for bridging pharmacokinetic drug interaction, and pharmacodynamic data between TAK 491 and TAK 536. The information content of the relevant sections in the package insert is however a review issue that will depend upon what the data show.

16. Does FDA agree with TGRD's proposed strategy for Module 2.7.2, including the differentiation between primary and supportive studies and the inclusion of all study reports in Module 5?

Preliminary Response

We agree.

17. Does FDA agree with TGRD's plan to summarize and assess cross-study comparisons with both TAK-491 and TAK-536 studies in Module 2.7.3?

Preliminary Response

We agree. It is not clear how informative the cross-study comparisons will be.

Information about TAK-536 is most relevant to safety concerns for TAK-491.

18. (b) (4)

Preliminary Response

No, 24-hour mean will not be included in the package insert. We are much more likely to want to include hourly average curves.

The Division would like to you to examine the change from baseline at the interdosing interval (trough) for the ABPM data. Final decisions on the labeling are review issues.

19. Does the FDA agree that placement of the ISE text portions in Section 2.7.3 and placement of tabular data portions in Section 5.3.5.3.1 are appropriate and adequate for FDA review?

Preliminary Response

We agree.

20. Does FDA agree with the overall efficacy pooling strategy?

Preliminary Response

We agree.

21. Does the FDA agree that the proposed pooling strategy and analysis plan will be sufficient to describe the efficacy of TAK-491 in the Black population?

Preliminary Response

Your proposal is acceptable.

22. Does the FDA agree that the statistical methods and data presentation summarized in this briefing document are adequate to support the FDA's efficacy review?

Preliminary Response

We agree.

23. Does FDA consider the strategy for including the TAK-536 safety data as supportive in the TAK-491 monotherapy NDA acceptable?

Preliminary Response

We agree.

24. Does FDA agree with TGRD's position that the safety information for the package insert (as outlined in the TPP, Appendix E) should come only from the TAK-491 phase 3 program, and not from the supportive studies?

Preliminary Response

This is a review issue.

25. Does FDA agree that it is acceptable not to include summaries and clinical study reports from the TAK-491CLD, TAK-491CCB, and TAK-536/pioglitazone clinical programs in the TAK-491 monotherapy CTD?

Preliminary Response

No. The Division requires you to submit summary safety information for these combination products, including any products dropped during development.

Discussion during Meeting

The sponsor presented the status of their clinical studies with the TAK-491/chlorthalidone (CLD) combination product to be included in the NDA (see slides 24-28). The Division agreed with the sponsor's proposal to include study reports from completed studies in the TAK-491/CLD, TAK-491CCB, and pioglitazone/536 programs in the NDA submission.

The sponsor noted that one study, 491CLD_306, will have final data available in time for the 120-day Safety Update. Dr. Stockbridge stated that key safety information, e.g., deaths, other serious AEs, discontinuations, and any other major safety findings, from this study should be included in the 120-day Safety Update; a full study report is not necessary.

26. Does the FDA agree with the plan to submit interim data for the 491_301 and 491-006 studies in the NDA; with a full CSR for 491_301 and a second interim clinical study report for 491-006 at the 120-day update?

Preliminary Response

We agree.

27. Does the FDA agree that the pooling strategy, statistical methods, and data presentation plans outlined in this briefing document are adequate to support the FDA's safety review and the proposed TPP?

Preliminary Response

On the surface, your proposal appears to be reasonable. However, upon review of the NDA, if an unexpected safety issue arises, additional analyses may be required.

28. Does the FDA agree with TGRD's approach for the Risk Management Plan (RMP)?

Preliminary Response

We agree.

Additional Comments

- We would appreciate a summary of the status of the TAK-536 development program (b) (4)

- Please submit the Clinical Pharmacology Summary according to the format specified in the attachment.
- It is not clear from the Briefing document whether you have conducted any pharmacometric analyses such as POPPK, Exposure-Response analyses. If you have conducted any pharmacometric analyses, please follow the format specified below:
Submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:
 - All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

Discussion during Meeting

(b) (4)



Clinical Pharmacology Summary

(b) (4)

The sponsor noted that CTD sections 2.7.1 (Summary of Biopharmaceutic Studies) & 2.7.2 (Summary of Clinical Pharmacology Studies) for the TAK-491 NDA submission are already underway to which Dr. Menon-Andersen responded that the Clinical Pharmacology Summary is not intended to result in a duplication of work. Therefore, it was the sponsor's discretion to include this document. However, it was noted that the document would assist the Division in its NDA review. Dr. Stockbridge suggested that the sponsor could alternately include an annotated version of the new template in Module 5 that links back to 2.7.1 and 2.7.2 appropriately. The sponsor agreed to follow up on the best way to the meet the Division's request.

Post-Meeting Note: In a November 6, 2009 email correspondence from Ms. Quynh Nguyen of DCRP to Ms. Deborah Yarbrough of TGRD, the Division agreed that the Clinical Pharmacology Summary could be submitted no later than the 120- day Safety Update as long as all other clinical pharmacology information is included in the NDA.

Pharmacometric analyses

TGRD presented an overview of the TAK-491 POPPK data that will be included in the NDA (see slide 30). The sponsor summarized that there are no data from the TAK-491 Phase 3 program. However, the sponsor plans to include population PK data from a Japanese Phase 2 TAK-536 study in the NDA. This was acceptable to the Division.

(b) (4)

(b) (4)

CONCLUSION

Agreement was reached regarding the content and format of an NDA submission for TAK-491. The sponsor plans to submit their NDA in April 2010.

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

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

Rd:
N Stockbridge 12/9/09
E Fromm- 12/9/09
T Marciniak 12/9/09
M Gordon 12/08/09
Menon-Andersen 12/08/09
C Resnick 12/8/09
P Gatti 12/7/09

IND 71,867
TAK-491 (azilsartan medoxomil)
Takeda
Page 11 of 64

Attachments:

Sponsor Presentation Slides
Clinical Pharmacology Summary
Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA
Submissions Template

30 Page(s) has been Withheld in Full as
B4 (CCI/TS) immediately following this
page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

ND-71867

GI-1

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DEVELOPMENT
CENTER INC

TAK-491

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
12/10/2009

Henry, Don

From: Yarbrough, Deborah (TGRD) [dyarbrough@tgrd.com]
Sent: Thursday, November 19, 2009 9:05 AM
To: Henry, Don
Subject: RE: Preliminary Responses

Don,

TGRD appreciates the detailed review of the pre-NDA briefing document and the thorough preliminary responses provided by FDA. TGRD understands the FDA responses to both of the questions and will take the recommendations into account when preparing the NDA. Because of the detailed feedback provided by FDA, TGRD feels that further discussion on these points is not necessary and requests that the CMC pre-NDA teleconference be cancelled.

Please let me know if you require formal communication to the IND to this effect. Thanks for your assistance,
Deb

Deborah Yarbrough, MS, MBA
Manager, Regulatory Affairs
Takeda Global Research & Development Center, Inc.
675 North Field Drive
Lake Forest, Illinois 60045
Phone: 847-582-3511
Cell: 847-207-3376
Fax: 847-582-2880

From: Henry, Don [mailto:Don.Henry@fda.hhs.gov]
Sent: Tuesday, November 17, 2009 4:25 PM
To: Yarbrough, Deborah (TGRD)
Subject: RE: Preliminary Responses

Deb,

Here are the preliminary responses for the teleconference meeting on Friday, November 20. There are a few items regarding the meeting that I would like to communicate:

- We will not be prepared to discuss any additional questions (or review any additional information) that were not in the meeting package.
- Provide any updates to the attendees list
- If these responses are clear to you and you feel there are no further discussions required, please contact me to let me know, and I will cancel the meeting.
- If there are still particular questions that need to be discussed, please inform me of which questions, prior to the meeting.

If you have any questions, please feel free to contact me

Thank you

Don

11/19/2009

From: Yarbrough, Deborah (TGRD) [mailto:dyarbrough@tgrd.com]
Sent: Tuesday, November 17, 2009 4:56 PM
To: Henry, Don
Subject: RE: Preliminary Responses

Hello Don,

This is the correct address. I look forward to receiving the Agency's preliminary comments!

Thanks,
Deb

From: Henry, Don [mailto:Don.Henry@fda.hhs.gov]
Sent: Tue 11/17/2009 3:50 PM
To: Yarbrough, Deborah (TGRD)
Subject: Preliminary Responses

Hello Deb,

I want to confirm that I have the correct email address to forward our preliminary responses. Please confirm receipt and that it is okay to forward our comments.

Thank you

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

###

This message is for the designated recipient only and may contain privileged or conf

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-71867

GI-1

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TAK-491

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

/s/

DON L HENRY
11/19/2009



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Takeda Global Research & Development Center, Inc.
Application Number:	IND 71,867
Product Name:	TAK-491 (azilsartan medoxomil)
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC), Pre-NDA
Meeting Date and Time:	Friday, November 20, 2009, 11:00 – 11:30 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	October 21, 2009

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled as a **teleconference meeting** on **Friday, November 20, 2009, from 11:00 – 11:30 ET** between **Takeda Global Research & Development Center, Inc.**, and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Don Henry, Regulatory Health Project Manager for Quality, 301-796-4227). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

1. BACKGROUND

Takeda Global Research & Development Center, Inc. (Takeda) has developed TAK-491 (azilsartan medoxomil) for the treatment hypertension. The product is currently in Phase 3 clinical trials. An End of Phase 2 meeting was held on June 16, 2008 to discuss Chemistry, Manufacturing and Controls (CMC). During the meeting, the Agency provided comments regarding the drug substance development program. Takeda has requested a Pre-NDA meeting to address these concerns.

2. DISCUSSION

- 2.1. **Briefing Package Question 1:** During the CMC EOP2 Meeting held between TGRD and FDA on 16 June 2008, FDA concluded that more rigorous impurity controls would be required for [REDACTED] (b) (4). Does FDA agree that the additional impurities controls (described in Section 2.6.2) are sufficient [REDACTED] (b) (4) [REDACTED] ?

FDA Response: *At this time we recommend a limit for each specified impurity* [REDACTED] (b) (4)

We recommend that any future NDA include the following:

- *structures of the specified impurities,* [REDACTED] (b) (4)

- 2.2. **Briefing Package Question 2:** During the CMC EOP2 Meeting (16 June 2008), [REDACTED] (b) (4)

Does FDA agree that TGRD has adequately accounted for the presence of all (b) (4) in the final drug substance?

FDA Response: (b) (4) (b) (4)



3. ADDITIONAL COMMENTS/ISSUES REQUIRING FURTHER DISCUSSION

No additional comments

4. CONCURRENCE:

{See appended electronic signature page}

Don Henry
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-71867

GI-1

TAKEDA GLOBAL
RESEARCH
DEVELOPMENT
CENTER INC

TAK-491

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

/s/

DON L HENRY
11/17/2009

RAMESH K SOOD
11/17/2009

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

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

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

From: Quynh Nguyen, PharmD, 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 with Sponsor

Application Number: INDs 71,867 (b) (4)
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:

Food and Drug Administration

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
(b) (4)	(b) (4)
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

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 (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 (b) (4) 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.

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-491CLD 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

(b) (4)

(b) (4)

(b) (4)
Monitors (APDs) and thought if

(b) (4)

(b) (4)

INDs 71,867 (b) (4)
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/
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Linked Applications

Sponsor Name

Drug Name / Subject

IND 71867

TAKEDA GLOBAL
RESEARCH
DEVELOPMENT
CENTER INC

TAK-491

(b) (4)

TAKEDA GLOBAL
RESEARCH
DEVELOPMENT
CENTER INC

TAK 491/CHLORTHALIDONE

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/s/

NORMAN L STOCKBRIDGE
06/22/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 71,867

Takeda Global Research & Development Center, Inc.
Attention: Deborah O. Yarbrough, MS, MBA
Program Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Yarbrough:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TAK-491, azilsartan medoxomil.

We also refer to the meeting between representatives of your firm and the FDA on June 16, 2008. The purpose of the meeting was to discuss designation of starting materials, drug substance specifications and stability protocol, drug product specifications and stability protocol and dissolution testing method.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Takeda Global Research and Development (TGRD)
Application Number:	IND 71,867
Product Name:	TAK-491
Meeting Requestor:	Deborah Yarbrough, MS, MBA
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC), End of Phase 2 (EOP2) Meeting
Meeting Date and Time:	Monday, June 16, 2008 1300 – 1400 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	March 20, 2008
Meeting Chair:	Kasturi Srinivasachar, Ph.D
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Division of Pre-Marketing Assessment III:

Kasturi Srinivasachar, Ph.D.; Pharmaceutical Assessment Lead

David Claffey, Ph.D.; Review Chemist

Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

EXTERNAL ATTENDEES:

Jeremy Baumann, Senior Pharmaceutical Scientist, CMC
Rosemarie Green, RPh Senior Project Manager, Project Management
Deborah Yarbrough, MS, MBA Program Manager, Regulatory Affairs

(b) (4)
Jay Ford, Director, Regulatory Affairs
Lily Pan, Intern, Regulatory Affairs

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) is developing TAK-491 (azilsartan medoxomil) under IND 71,867. TAK-491 is a prodrug that is hydrolyzed completely to the active moiety, TAK-536 (IND (b) (4)), an angiotensin II AT I receptor blocker (ARB). TAK-491 is in development for the treatment of mild to moderate hypertension, alone or in combination with other anti-hypertensive agents. Deborah O. Yarbrough, MS, MBA, Program Manager, Regulatory Affairs for TGRD requested a Type B Chemistry, Manufacturing and Controls (CMC) End of Phase 2 (EOP2) meeting on April 14, 2008, to discuss designation of starting materials, drug substance specifications and stability protocol, drug product specifications and stability protocol and dissolution testing method. The meeting was granted on April 17, 2007, by Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, Office of New Drug Quality Assessment (ONDQA). The meeting was scheduled as a teleconference for June 16, 2008, 1300-1400 EDT. The corresponding briefing package that provided additional information regarding discussion topics and specific questions was submitted by TGRD on May 15, 2008. The preliminary responses to the questions contained in the briefing package were archived and shared with TGRD on June 10, 2008 to promote a collaborative and successful discussion at the meeting. The teleconference occurred as scheduled on June 13, 2008. The minutes of the teleconference are recorded below.

TGRD discussion topics:

- Designation of starting materials
- Drug substance specifications and stability protocol
- Drug product specifications and stability protocol
- Dissolution testing method.

2.0 DISCUSSION

2.1 Briefing Package Question 1: Does the Agency agree that there is sufficient justification to designate (b) (4),?

FDA Response: There is sufficient justification (b) (4).
(b) (4)

Meeting Discussion: TGRD acknowledged receipt of FDA's response. TGRD committed to providing additional scientific support regarding evaluation of analytical methods and specifications for the detection of impurities in (b) (4) to assure control of impurities carrying over into the drug substance. FDA indicated that the adequacy of the methods and specifications is a data driven review issue to be evaluated during the NDA review cycle and that a decision on the appropriateness of (b) (4) can not be made at this time.

2.2 Briefing Package Question 2: The specifications for drug substance include requirements for appearance, identification, heavy metals, related substances, residual solvents, (b) (4) and assay (content). Does the Agency agree that the specifications are adequate to demonstrate satisfactory quality for the TAK-491 drug substance?

FDA Response: We recommend the following changes:

- Recommend the reinstatement of the potassium identification test or provide evidence that the identification tests are specific for the potassium salt (b) (4).

Meeting Discussion: TGRD acknowledged receipt of FDA's response and committed to include sufficient scientific justification to support the use of the FTIR for potassium identification. In particular, these data will demonstrate the method's specificity for the potassium cation. No further discussion occurred during the meeting.

- Recommend that the acceptance criteria for all unidentified impurities be lowered to the ICH Q3A recommended identification threshold (0.10%) and that the acceptance criterion for all other specified impurities should be (b) (4) unless their levels have been qualified by toxicological or ADME studies.

Meeting Discussion: TGRD acknowledged receipt of FDA's response. TGRD committed to develop and justify specifications based on their data. No further discussion occurred during the meeting.

- Considering the (b) (4) drug substance's hygroscopicity and aqueous insolubility, details of its (b) (4) screening should be provided. Recommend the inclusion of a (b) (4) test at release or justification for its absence.

Meeting Discussion: TGRD acknowledged receipt of FDA's response and committed to include sufficient scientific justification in the NDA. No further discussion occurred during the meeting.

- Recommend the addition of a limit for total impurities (b) (4).

Meeting Discussion: TGRD acknowledged receipt of FDA's response and committed to providing a limit for total impurities (b) (4). The Agency clarified that the request for the inclusion of a limit for total impurities (b) (4) was to ensure that the total level of impurities (b) (4) did not reach excessively large levels. TGRD also committed to providing justification for the relatively broad acceptance criterion for drug substance assay.

2.3 Briefing Package Question 3: Does the Agency agree that TGRD's plan for the API stability data to be provided in the NDA will support commercialization?

FDA Response: This proposal appears adequate however this will be a review issue. Ensure that the drug substance stability protocol includes a commitment to test one batch annually. (as recommended by the ICH Q7 guidance).

Meeting Discussion: TGRD acknowledged receipt of FDA's response and agreed with FDA's recommendation. No further discussion occurred during the meeting.

2.4 Briefing Package Question 4: Based upon the current drug product specifications in place and the planned modifications, does the Agency consider these tentative specifications appropriate for future commercialization of TAK-491 tablets?

FDA Response: We recommend the following changes to the drug product specifications:

- Ensure that the commercial tablets include imprinting as per regulatory requirements (i.e. ensure that they are not 'plain' as described in the appearance specification).

Meeting Discussion: TGRD acknowledged receipt of FDA's response. TGRD stated that the commercial product would be embossed in accordance with regulatory guidelines. No further discussion occurred during the meeting.

- Strength specific acceptance criteria for other individual impurities are inappropriate as if, for example, one 80 mg strength tablet were to be substituted with two 40 mg strength tablets the patient would have the potential to be exposed to a greater amount of degradants. Therefore, we recommend that unidentified impurities have an acceptance criterion of (b) (4) limit for each of the strengths ((b) (4)) and any impurities present at levels above the ICH recommended levels for reporting, identification or qualification be justified by data from toxicological or ADME studies.

Meeting Discussion: TGRD acknowledged receipt of and agreed with FDA's response. No further discussion occurred during the meeting.

- Recommend the addition of tests for tablet hardness and (b) (4) as these criteria appear to impact drug product stability.

Meeting Discussion: TGRD acknowledged receipt of FDA's response, including the observation that (b) (4) is considered a critical process parameter. TGRD committed to evaluate the tests recommended by FDA during the generation of the registration data and to provide scientific justification regarding the inclusion or exclusion of the specification in the final specifications. No further discussion occurred during the meeting.

2.5 Briefing Package Question 5: Based upon the dissolution method development history, does the Agency agree that the method selected by TGRD is appropriate to be utilized in the registration stability studies and would be considered as a potential regulatory control method?

FDA Response: It is unclear how this method can be considered appropriate at this time considering the significant drug substance degradation in the modified (pH 7.8) dissolution medium. Further, it appears that a UV assay (rather than an HPLC assay) is used to quantify the degree drug substance dissolution. It is unclear if (and how) the degradation product(s) are accounted for in this assay as these species will likely have different extinction coefficients.

Meeting Discussion: TGRD acknowledged receipt of FDA's response. (b) (4)
(b) (4)
TGRD committed to providing further data to support the selection of dissolution media, pH and the inclusion or exclusion of (b) (4) in the NDA, to support the proposed dissolution method. FDA recommended that TGRD use a time point (b) (4) as such a time point would appear to be more discriminatory during the stability program. TGRD and FDA agreed that the specifications would be based on the observed data included in the NDA. TGRD acknowledged that their dissolution method has not been demonstrated to be discriminatory to manufacturing or formulation variations.

2.6 Briefing Package Question 6: The proposed commercial drug product packaging contains specific technologies to control moisture. Does the Agency agree that TGRD's plan for packaging and drug product stability data to be provided in the NDA will support commercialization of TAK-491 tablets?

FDA Response: The proposed approach appears appropriate however this will be a review issue. The CoA from the validation lots should be provided to the Agency as soon as they are available.

Meeting Discussion: TGRD acknowledged receipt of FDA's response. TGRD committed to submit the Certificate of Analysis as soon as it was available. FDA indicated that site specific data was not necessary for expiry dating. No further discussion occurred during the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time

4.0 ACTION ITEMS

There are no other action items other than those recorded in the meeting discussion section for each question.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Kasturi Srinivasachar, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Linked Applications

Sponsor Name

Drug Name

IND 71867

TAKEDA GLOBAL
RESEARCH
DEVELOPMENT
CENTER INC

TAK-491

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

/s/

SCOTT N GOLDIE
07/10/2008

KASTURI SRINIVASACHAR
07/10/2008

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

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Transmitted via email to: dyarbrough@tgrd.com

Attention: Ms. Deborah Yarbrough

Sponsor: Takeda Global Research &
Development Center, Inc.

Phone: (224) 554-6354

Subject: EOP2 Meeting Minutes

Date: June 4, 2007

Pages, including this sheet: 13

From: Quynh Nguyen, Pharm.D.
Phone: 301-796-0510
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Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

End-of-Phase 2 Meeting with Sponsor

Application Number: IND 71,867
Sponsor: Takeda Global Research & Development Center, Inc.
Drug: TAK-491
Type of Meeting: End-of-Phase 2
Classification: B
Meeting Date: April 26, 2007
Briefing Package Received: March 26, 2007
Confirmation Date: February 23, 2007
Meeting Request Received: February 15, 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
Abraham Karkowsky, M.D., Ph.D.	Deputy Director (Acting) and Medical Team Leader, Division of Cardiovascular and Renal Products (DCRP)
Akinwale Williams, M.D.	Medical Officer, DCRP
Stephen Grant, M.D.	Medical Officer, DCRP
Valeria Friedlin, Ph.D.	Statistician, Division of Biometrics I
Peter Hinderling, M.D.	Clinical Pharmacologist, Office of Clinical Pharmacology
Charles Resnick, Ph.D.	Pharmacology Team Leader, DCRP
Donald Jensen, Ph.D.	Pharmacologist, DCRP
Barbara Radziszewska, Ph.D.	Reviewer, Division of Cardiovascular Devices, CDRH
Devi Kozeli	Project Specialist & Assistant to the Division Director, 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
Aziz Karim, Ph.D.	Vice President, Clinical Research – Phase 1
Karen Asin, Ph.D.	Associate Director, Nonclinical Safety and Efficacy
Guoliang “Charlie” Cao, Ph.D.	Senior Manager, Biometrics and Data Management
Rosemarie Green, R.Ph.	Senior Project Manager, Project Management

(b) (4)	(b) (4)
Deborah Yarbrough, M.S., M.B.A.	Program Manager, Regulatory Affairs
Timothy Farber	Associate, Regulatory Affairs

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. This End-of-Phase-2 meeting was scheduled to discuss the proposed Phase 3 clinical development program for

TAK-491. The Division's Preliminary Responses were sent to the sponsor on April 24, 2007. The sponsor agreed with the Division's Preliminary Responses to Questions 2, 3, 4, 7, 8 and 9. Therefore, the purpose of this meeting was to clarify Figure 3.a and Table 3.d in the meeting package and to discuss Questions 1, 5, and 6 as noted below.

DISCUSSION

Preliminary Response

We note that Figure 3.a (page 25) and Table 3.d (page 26) of the meeting package do not seem to agree. Please clarify.

Discussion during Meeting

The sponsor explained that for Figure 3.a, the left panel represented the plasma concentrations of TAK-536 and the right panel represented the plasma concentrations of TAK-536 M-II. M-II is inactive at the angiotensin II type 1 receptor. Based on the figures, the Agency commented that the data support the rationale for avoiding high peak concentrations of TAK-536 by giving TAK-491. The sponsor stated that after correcting for differences in molecular weight between TAK-536 and TAK-491 and 10-15% lower bioavailability of TAK-491, the TAK-536 plasma exposures are the same. A 40 mg dose of TAK-536 is equivalent to about a 65 mg dose of TAK-491.

The Agency commented that the pharmacokinetics did not make it look like TAK-491 was a QD drug and asked if the sponsor had done a BID study, noting that BID dosing had improved the effects of losartan. The sponsor replied that they had not studied BID dosing, but would consider the Agency's comments. The sponsor also added that ABPM data indicate good durability of blood pressure reduction over 24 hours with QD dosing of TAK-491.

Clinical Pharmacology

1) Does the Agency concur that the proposed TAK-491 doses and the overall study design for the planned QTc study are adequate?

TGRD plans to conduct a thorough QTc study using a single-blind, crossover design and applying analysis and interpretation principles specified in *Guidance for Industry – E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October 2005*. The highest therapeutic dose of TAK-491 is anticipated to be 80 mg; therefore, TAK-491 160 mg and 320 mg doses are being proposed for this study. Additionally, comparators will be placebo, as well as 400 mg dose of moxifloxacin as the positive control. The primary endpoint of this study will be change from Baseline to Final Visit of dosing (Day 6) for QTc interval (Fredericia correction). Categorical analyses will also be conducted to evaluate the proportion of subjects exceeding predefined upper limit values.

Preliminary Response

The lack of detail in your proposal precludes us from making any specific comments. We will provide specific comments when you submit the protocol for your proposed QTc study. We have the following general comments:

1. In order for the proposed QTc study to be of value, the exposures achieved at the highest dose should, at a minimum, be as high as the highest exposures that could possibly be attained after administration of the to-be-marketed dose(s). Therefore, prior to designing your "thorough QT/QTc study", you should have a good understanding of factors that will increase patient exposure to TAK-536 (e.g., effects of metabolic inhibitors) and to its principal metabolites.

Simply choosing doses that are some multiple of what is currently thought to be the therapeutic dose is not adequate.

2. We recommend you incorporate the following elements into your assessment of the ECGs recorded during this study:
 - a. Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation,
 - b. Blinding of ECG readers to subject identifiers, treatment, time, and day (i.e., Day -1; Day 1),
 - c. Review of all ECGs from a particular subject by a single reader on a single day, and
 - d. Assessment of inter-reader variability by having a subset of tracings interpreted by a second reader.
3. In order to minimize the effect of phlebotomy on QT measurement, we recommend that you include venipunctures during baseline ECG sampling on Day -1.
4. In addition to the primary statistical analysis of the data as defined by the ICH E14 guidance, we recommend using a linear/nonlinear mixed effects modeling approach to quantify the relationship between the plasma concentration and ddQTc (time-matched placebo and baseline- adjusted QTc) interval and to estimate the expected ddQTc and its 90% confidence interval at relevant concentration levels, e.g., the mean maximum plasma concentrations under therapeutic and suprathreshold doses or other concentrations of interest. This should be done for each analyte (e.g., parent, any metabolite(s)).

In addition to fitting a direct pharmacodynamic model (without a delay between concentration and effect) to the data, the need for a delayed-effect model should also be evaluated (via graphical displays and/or model estimation). Please provide justification for your choice of pharmacodynamic model. If necessary, individual predicted concentrations can be used to drive the pharmacodynamic model. All model codes and data sets to support this analysis should be submitted as a SAS transport files (*.xpt) for review.

5. At the time of the thorough QT study report submission, the following items should be submitted:
 - a. Electronic or hard copy of the study report
 - b. Electronic or hard copy of the clinical protocol
 - c. Electronic or hard copy of the Investigator's Brochure
 - d. Annotated CRF
 - e. A Define file which describes the contents of the electronic data sets
 - f. Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
 - g. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - h. A completed Highlights of Clinical Pharmacology Table (see Table 1 below)

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

Discussion during Meeting

The Agency provided the following recommendations for the TAK-491 QTc study:

- If there is no accumulation of drug or metabolites after single and multiple doses of TAK-491, low variability among subjects in serum drug concentration in relation to dose, and no observed or expected drug interactions resulting in substantially increased Cmax, then the sponsor could consider conducting a single dose study. This recommendation is also supported by the lack of a signal from the nonclinical studies.

- Dr. Grant suggested a straightforward, 4 period cross-over study (placebo, positive control, intermediate high dose, and highest dose) might be feasible. He also recommended that the study be double-blind. On Day-1, the sponsor should collect ECGs and perform all other procedures at the same times as on the treatment Day 1 (control for time of day, venipuncture, fluids, etc.). A safety ECG should be conducted on the day after treatment and can be read separately from other ECGs. After a one week washout, the same procedure should be done for the next treatment period. A three-arm study (placebo, positive control, and highest dose) could be conducted if the sponsor is confident that QT prolongation will not be a problem.
- The Agency agreed that a top dose of 320 mg appears adequate after confirmation that accumulation of the drug and metabolites are unlikely because the half-lives of the drug and all metabolites are short and significant drug-drug interactions are unlikely.
- A double delta comparison to both the subjects' own baseline and to placebo was recommended.
- Dr. Grant emphasized that the reading procedure should be consistent with the recommendations in the ICH E14 guideline so that bias in interpreting the QT intervals is not introduced. All the ECGs should be stored until study completion. ECG readers should be blinded to subject identification, treatment assignment and period. Interpretation of a single subject's ECGs should be ideally performed in one sitting to minimize intra-reader variability in interpretation.
- Multiple correction formulae should be used to calculate QTc. Typically, QTc by the Fredericia formula is stipulated the primary analysis but may be inadequate if the drug affects heart rate.
- The sponsor should provide narratives and case reports for any cases of death, syncope, seizures, SAEs, serious ventricular arrhythmias, and AEs leading to withdrawals.
- The sponsor should submit the study protocol to the IND as a normal protocol for review and not as a Special Protocol Amendment (SPA). The Agency would be willing to review the study report prior to filing of the NDA.

Clinical Development Plan

Dose-Rationale

2) *Does the Agency agree that the doses selected are appropriate for the proposed phase 3 studies?*

Recent studies demonstrate the pharmacokinetic profile of the commercial tablet formulation of TAK-491 is equivalent to that of the TAK-536 tablet (Section 3.3). Therefore, the dose selection for the phase 3 clinical program is dependent primarily on the results of the TAK-536 tablet dose-ranging study (01-04-TL-536-002). The results of the TAK-491 capsule dose-ranging study (01-05-TL-491-005) further support the dose selection. The proposed phase 3 doses are 20 mg, 40 mg, and 80 mg of TAK-491 tablets based on the following considerations.

The TAK-491 capsule has a pronounced food effect response, resulting in higher TAK-536 bioavailability when taken with high-fat content meals. In contrast, the TAK-536 tablet has a negligible food effect. Furthermore, the TAK-536 pharmacokinetic profile associated with the TAK-491 capsule administration results in lower maximum observed concentration (C_{max}) and higher minimum observed plasma concentration (C_{min}) values compared to the TAK-536 tablet, consistent with a controlled-release profile. However, the results of the recent TAK-491 tablet vs capsule bioavailability study (01-05-TL-491-015) suggest that this pharmacokinetic profile is specific to the capsule formulation and not an intrinsic property of TAK-491. This study demonstrated that the TAK-491 tablet has 70% greater bioavailability than that of the TAK-491 capsule and that the TAK-491 tablet does not show any significant food-effect response or controlled-release profile.

In follow-up to the results of the TAK-491 tablet vs capsule bioavailability study (01-05-TL-491-015), TAK-536 bioavailability after administration of the TAK-491 tablet and TAK-536 tablet was compared (01-06-TL-491-017). The results of this study indicated that plasma concentration-time curves of TAK-536 are similar following administration of the TAK-491 tablet and TAK-536 tablet. This finding is consistent with the additional observation that the metabolic ratios (area under the plasma concentration-time curve [AUC] TAK-536 M-II)/(AUC TAK-536) are similar after administration of TAK-491 or the TAK-536 tablet, indicating similar disposition kinetics. The results of this study further suggest that TAK-491 tablet dissolution and conversion to TAK-536 is very rapid, such that there is no meaningful difference between TAK-491 and TAK-536 tablets with respect to TAK-536 systemic exposure, after adjusting for molecular weight and a small difference in bioavailability (Section 3.3).

The lack of bioequivalence between the TAK-491 tablet and capsule reduces the applicability of the TAK-491 capsule dose-ranging study for phase 3 dose selections of TAK-491 tablets. In contrast, the equivalence of the TAK-491 and TAK-536 tablets substantially strengthens the applicability of the TAK-536 dose-ranging study to guide phase 3 dose selections for TAK-491 tablets. Based on the results of the TAK-491 tablet vs TAK-536 tablet bioavailability analysis (01-06-TL-491-017), the ratio between equal doses of TAK-491 and TAK-536 tablets for TAK-536 systemic exposure (AUC) is 0.62. Thus, on a mg-mg basis, the TAK-491 equivalent tablet dose based on TAK-536 exposure is approximately twice that of TAK-536 tablets (Section 3.3).

The most reliable data from the TAK-536 and TAK-491 dose-ranging studies are the parameters derived from ambulatory blood pressure monitoring (ABPM) because these data represent integrated blood pressure throughout the day and are not confounded by variables such as “white coat” hypertension or ascertainment bias. The latter principle is reinforced by the observation in the TAK-536 and TAK-491 dose-ranging studies that the placebo effect for the ABPM parameters was negligible, in contrast to the relatively large placebo effect observed for clinic blood pressure parameters. ABPM parameters also are clinically more predictive of cardiovascular outcome than clinic blood pressure measurements, as demonstrated by numerous studies. In particular, mean 24-hour SBP is the best predictor of cardiovascular risk, even after adjustment for other risk factors that include clinic blood pressure. As such, mean 24-hour SBP will be the primary endpoint for most of the phase 3 trials with TAK-491. Based on the ABPM results from the TAK-536 and TAK-491 dose-ranging studies, the proposed phase 3 doses of TAK-491 tablets are 20 mg, 40 mg, and 80 mg. The mean 24-hour SBP data from the TAK-536 dose-ranging study indicate that blood pressure reduction reached plateau at 20 mg to 40 mg; mean 24-hour DBP data are completely consistent with the SBP data. These TAK-536 doses are similar to TAK-491 doses of 40 and 80 mg. Notwithstanding the differences between the TAK-491 capsule and tablet formulations, the TAK-491 capsule dose-ranging study results support the TAK-536 dose-ranging results; 24-hour mean SBP and DBP data indicate that TAK-491 doses higher than 40 to 80 mg would not confer additional blood pressure reduction.

Preliminary Response

We agree that the doses selected appear reasonable based on the results of the previous studies.

Phase 3 Clinical Development Plan

3) *Does the Agency agree that the study designs are adequate to fully characterize the antihypertensive efficacy and safety of TAK-491?*

The phase 3 clinical development plan consists of 9 studies: 1 monotherapy study, 2 coadministration studies, a Black population study, 3 active comparator studies, and 2 long-term safety studies (Section 5.3.1).

- Monotherapy study (01-05-TL-491-008) will evaluate the efficacy and safety of TAK-491

- (20, 40, and 80 mg) vs placebo and olmesartan 40 mg, over an 8-week treatment period.
- Black population study (01-05-TL-491-011) will evaluate 40 mg and 80 mg TAK-491 vs placebo for 8 weeks.
 - Two coadministration studies (1 with chlorthalidone 25 mg [01-05-TL-491-009] and 1 with amlodipine 5 mg [01-05-TL-491-010]) will evaluate the efficacy and safety of TAK-491 (40 mg and 80 mg) coadministered with chlorthalidone or amlodipine, respectively, compared with chlorthalidone or amlodipine alone, over an 8-week treatment period.
 - The 8-week ARB comparator study (01-06-TL-491-019) will compare TAK-491 40 mg to 80 mg with olmesartan 20 mg to 40 mg and valsartan 160 mg to 320 mg.
 - Two additional comparator studies will evaluate longer-term efficacy and safety of TAK-491 by comparing TAK-491 40 mg and 80 mg to valsartan 160 mg (TAK-491_301) or ramipril 10 mg (01-05-TL-491-020), respectively, over a 6-month treatment period.
 - Two long-term, open-label safety studies, one 13 months (01-05-TL-491-006) and the other 7 months (01-05-TL-491-016) in duration, will be conducted to assess the safety and tolerability of TAK-491 40 mg and 80 mg. The 7-month safety study will include a 6-week, double-blind reversal phase to further evaluate the durability of TAK-491 efficacy.

Preliminary Response

Please clarify whether study 01-05-TL-491-016 includes a placebo-controlled withdrawal phase.

Since you have not performed specific studies in subjects with renal impairment, we recommend that you exclude subjects with $Cl_{cr} < 30$ mL/min.

4) *Does the Agency agree that the studies presented in the phase 3 clinical plan are sufficient to support the proposed indication: "TAK-491 is indicated for the treatment of essential hypertension alone or in combination with other antihypertensive agents"?*

This question is based on the assumption that the outcomes of the studies in the phase 3 clinical plan (Section 5.3.1) for the proposed indication are positive (i.e., the results of the primary endpoints of TAK-491 are significantly more efficacious than placebo), and an acceptable safety profile consistent with the overall program and class is observed. The primary efficacy endpoints are mean value of 24-hour SBP derived from ABPM in five 8-week studies and the trough, sitting, clinic DBP in two 6-month comparator studies.

Preliminary Response

We agree.

Phase 3 Statistical Analysis Plan

5) *Does the Agency agree with the proposed choices and definitions of the analysis populations for placebo and active comparator trials, and the use of the principle of last observation carried forward (LOCF) for the modified intent-to-treat populations?*

The analysis population (Section 5.4.1) for the phase 3 studies is represented by 3 groups:

- Full Analysis Set (FAS): defined as all randomized subjects that received 1 dose of double-blind study medication and having a baseline value and at least 1 treatment value.
- Per Protocol Set: defined as all subjects included in FAS, except for major protocol violators.
- Safety Analysis Set: defined as all subjects who received at least 1 dose of study medication.

The FAS will be the primary data set used for the efficacy analyses, while supportive efficacy analyses, as appropriate, will be conducted using the per protocol set. All routine safety analyses will be based on the

safety analysis set. Intent-to treat populations with no available efficacy data will be analyzed using an imputed value defined by the LOCF.

Preliminary Response

We agree. However, if the number of dropouts is not small, then an issue of the potential asymmetric dropout rates arises and needs to be considered carefully. We urge that all dropouts should be followed up for the primary endpoint and those secondary endpoints that you plan to show in the labeling. If there are still a substantial number of dropouts, then an alternative imputation method and/or sensitivity analysis method should be explicitly proposed in the SAP to demonstrate the robustness of the primary efficacy results.

Discussion during Meeting

The Agency agreed with the sponsor's proposal to classify 20% or more dropouts in any arm as being "not small."

There was discussion regarding why the sponsor chose to conduct an 8-week trial versus a shorter, 6-week trial. The Agency was concerned with not having an ABPM measurement between baseline and the Week 8 visit as subjects who drop before the Week 8 visit would have no ABPM measurement for comparison. The Agency suggested that shortening the study duration could mitigate the issue of asymmetrical withdrawal and would be in line with its recommendation for conducting shorter trials. Dr. Temple suggested that a treatment period of 4 or 6 weeks may be adequate, as long as TAK-491 reaches plateau within this time period. The sponsor agreed to review the data to determine if studies could be shortened and preliminarily proposed a 6 week study duration based on attainment of plateau by this time. The Agency and sponsor agreed that the comparison study (019) could remain an 8-week trial because of the 2-week titration period prior to reaching the maximum dose of each therapeutic agent.

The sponsor agreed to perform a sensitivity analysis if the dropout rate is 20% or more in any arm based on the observed data. Dr. Temple suggested that if interim ABPM values were scheduled at 2 and/or 4 weeks, then there probably would not be any missing data. The sponsor replied that the protocols specify ABPM be conducted for early withdrawal, but acknowledged that the probability of obtaining a final on-treatment ABPM in this situation is low. There was agreement that data from follow-up periods (i.e., off-treatment) would not be usable for the primary endpoint since those data would not be clean. The sponsor pointed out that ABPM is not a trivial procedure and that the burden of an interim 24-hour ABPM procedure could compromise study compliance. Dr. Temple commented that the precision of ABPM was so great that the sponsor may not need such a large sample size in the 008 study. The sponsor explained that the sample size is driven by the small treatment difference expected between TAK-491 and olmesartan (relative to the expected difference between TAK-491 and placebo).

The sponsor summarized its plans by saying that the dropout issue would be handled by considering a shorter study duration and sensitivity analysis on clinic BP rather than adding an interim ABPM, and the Agency concurred with this strategy.

6) Does the Agency agree with the choice of primary and secondary efficacy endpoints and the proposed testing methodology for controlling type I error?

The primary efficacy endpoints in the five 8-week studies will be mean value of 24-hour SBP by ABPM. The selection of 24-hour SBP by ABPM as primary endpoint in those studies is based on the weight of evidence indicating that this parameter is the best predictor of cardiovascular risk, even after adjustment for other risk factors, including clinic blood pressure. The primary analysis method will be analysis of covariance (ANCOVA) with effect for treatment and baseline as covariate on mean change in 24-hour SBP from Baseline to the last scheduled study visit or the last on-treatment visit if the subject did not

complete the study. The main secondary efficacy endpoint is mean 24-hour DBP by ABPM and will be analyzed using ANCOVA. Other ABPM parameters and trough, sitting clinic DBP will also be evaluated as a secondary efficacy endpoints. Trough, sitting clinic DBP will be utilized as the primary endpoint in the 2 longer term 6-month efficacy studies; the longer treatment period and thus higher probability of withdrawals makes ABPM measurements less practical. Either stepwise or closed testing methodology will be implemented in some studies to control for type 1 error (Section 5.4).

Preliminary Response

For Study #011 with two doses of TAK-491 and placebo, we agree with the proposed “closed” procedure for the primary efficacy analysis.

However, for Study #008 with three TAK-492 doses, one olmesartan arm and a placebo arm, the secondary endpoints also include comparisons of olmesartan to TAK-491. If you plan to include any claims on comparisons of TAK-491 to olmesartan in the labeling, then controlling type one error for the secondary endpoints will be needed. If the primary endpoint wins for all three TAK-491 doses versus placebo, then a hierarchical testing procedure for the secondary endpoints will do the job. However, if the primary endpoint does not win for all three TAK-491 doses versus placebo, then controlling the strong family-wise error can be quite complicated for the secondary endpoints. In the active comparator Study #019, controlling type one error for the secondary endpoints will also be needed. You will need to submit a detailed plan of resolving the multiplicity problem for the secondary endpoints in Studies #008 and #019.

Discussion during Meeting

The sponsor confirmed that the proposed 24-hour mean SBP by ABPM as primary endpoint was acceptable to the Agency. The sponsor stated that the Type 1 error was controlled for the comparison between TAK-491 and placebo on primary endpoint. The Agency accepted the plan for the 011 study, which has no active comparator. For the 008 study with olmesartan as a comparator, the plan would be acceptable if no superiority claims are expected. If the sponsor wished to claim superiority over olmesartan, then the analysis plan will be needed to control for Type 1 error. The sponsor must deal with the potential multiplicity issue: the primary comparison (against placebo, high dose down to low dose) must win first and then the comparison starting with the high dose of TAK-491 against olmesartan could proceed. If the sponsor was convinced that TAK-491 will win on all three doses against placebo, then there will not be a problem proceeding to the olmesartan comparison. However, if, for example, the 20 mg dose does not beat placebo, then the sponsor cannot consider the olmesartan comparisons based on the current methodology. (b) (4)

(b) (4)

The sponsor asked if the control of Type 1 error for the secondary endpoint was for comparison between TAK-491 and olmesartan, and the Agency confirmed that this was the case. The Agency also agreed that for the 019 study with only one TAK-491 dose, the current sequential testing procedure was acceptable. The Type 1 error controls for the other studies were also acceptable.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Subject Exposure

7) *Does the Agency agree that the overall subject exposure is adequate to support the proposed monotherapy and coadministration indications?*

Subject exposure will be determined for TAK-491 for overall subject exposure, for healthy versus non-healthy subjects, and for the proposed phase 3 clinical program. In completed phase 1 and phase 2 clinical studies, 549 subjects have been exposed to TAK-491 and 870 subjects have been exposed to TAK-536. Another 3670 subjects will be exposed to TAK-491 in planned phase 3 studies (Section 5.5). Among them, 1480 subjects will be randomized into 6-month studies and 300 subjects into the 1-year safety study.

Preliminary Response

We agree.

Nonclinical Questions

8) *Does the Agency agree that the data from the TAK-536 52-week repeat dosing dog study can be bridged to the TAK-491 program to satisfy the 9-month repeat dosing dog toxicity study requirement?*

Reference is made to the TAK-491 EOP1 meeting held on 6 April 2006. At this meeting, the Agency agreed to review the data from the TAK-491 and TAK-536 26-week dog studies to determine if the results of these studies were sufficiently similar so as to allow bridging of the 52-week dog study conducted with TAK-536 to the TAK-491 development program. Per the agreement at the EOP1 meeting, the Agency would allow TGRD to bridge the 52-week dog study conducted with TAK-536 (Report No. TAK-536/C-46-263 plus TAK-536/C-46-267) to the TAK-491 program if supported by a similarity in findings from the 26-week studies. Both the TAK-491 and TAK-536 26-week dog studies (TAK-491/00-166 and TAK-536/C-46-263 plus TAK-536/C-46-267, respectively) were submitted to the TAK-491 IND in Serial No. 027 on 22 September 2006.

Preliminary Response

We agree.

9) *TGRD would like to fully understand the rationale behind the Division's position regarding the carcinogenicity testing requirements for TAK-536 M-II. Will the Division further discuss the requirement for the 2-year bioassay to be included in the NDA package and explore other submission options with TGRD?*

Reference is made to the series of correspondence between TGRD, DCRP, and E-CAC regarding the carcinogenicity testing requirements for TAK-491 and TAK-536 M-II. Agreement was reached that

carcinogenicity studies would be conducted in mice and rats, for both TAK-491 and TAK-536 M-II. Each compound would be evaluated individually through the conduct of 6-month TgrasH2 mouse assays and standard 2-year rat bioassays. Reference is made to the E-CAC meeting held on 5 September 2006. In the resulting meeting minutes, E-CAC stated that it could be appropriate for the Division to consider approval of the drug following review of the first studies (ie, 6-month TgrasH2 mouse assays for TAK-491 and TAK-536 M-II) but while the second studies (ie, 2-year rat bioassays for TAK-491 and TAK-536 M-II) were still underway. However, in follow-up correspondence, DCRP did not concur with the E-CAC proposal.

Preliminary Response

We remain unable to identify a reason why an exception should be made in order to approve your drug prior to completion of routine carcinogenicity testing in two species.

CONCLUSION

This End-of-Phase-2 meeting was scheduled to discuss the proposed Phase 3 clinical development program for TAK-491. The purpose of the meeting was to clarify Figure 3.a and Table 3.d in the meeting package and to discuss Questions 1, 5, and 6.

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

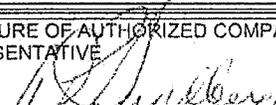
Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Rd:
R Temple 6/1/07
A Williams 5/21/07
V Freidlin 5/29/07
S Grant 5/29/07
D Kozeli 5/21/07

**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
6/6/2007 03:05:20 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET				
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugs/default.htm					
1. APPLICANT'S NAME AND ADDRESS TAKEDA PHARMACEUTICALS NOR AMER Clint Johansen ONE TAKEDA PARKWAY DEERFIELD IL 60015 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 290-796				
2. TELEPHONE NUMBER 847-582-2078	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:				
3. PRODUCT NAME azilsartan medoxomil	6. USER FEE I.D. NUMBER PD3010048				
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: <table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 </td> <td style="width: 33%; vertical-align: top;"> Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 </td> <td style="width: 33%; vertical-align: top;"> An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. </td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE SUP Reg. Aff.	DATE 23 Feb 2010			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$1,405,500.00					
Form FDA 3397 (03/07)					

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