

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

22-100

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

AMENDED PATENT CERTIFICATIONS UNDER 21 CFR 314.50(i) AND SECTION 505(b)(2)(A) [21 U.S.C. 355(b)(2)(A)]

Applicant hereby certifies the following with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a drug (the drug product or drug substance that is a component of the drug product) on which investigations that are relied upon by the Applicant for approval of its application were conducted, or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the Act and §314.53:

In the opinion of Applicant, and to the best of its knowledge, there are two patents (U.S. 4,572,909 and 4,879,303) that claim amlodipine besylate (Norvasc® NDA 19-787) on which investigations that are relied upon by Applicant for approval of its application were not conducted by or for Applicant and for which Applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted, or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the Act and §314.53. Those patents are listed in

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the Orange Book for Norvasc® (NDA 19-787). With respect to those patents, Applicant certifies, in its opinion, and to the best of its knowledge as follows:

PARAGRAPH II CERTIFICATION FOR U.S. PATENT 4,572,909

In Applicant's opinion, and to the best of its knowledge, U.S. Patent 4,572,909 has expired.

PARAGRAPH III CERTIFICATION FOR U.S. PATENT 4,879,303

In Applicant's opinion, and to the best of its knowledge, U.S. Patent 4,879,303 will expire on March 25, 2007.

In the opinion of Applicant, and to the best of its knowledge, there are two patents (U.S. 5,616,599 and 6,878,703) that claim olmesartan medoxomil (Benicar® NDA 21-286) on which investigations that are relied upon by Applicant for approval of its application were conducted, or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the Act and §314.53. Those patents are listed in the Orange Book for Benicar® (NDA 21-286). With respect to those patents, Applicant certifies as follows:

PARAGRAPH IV CERTIFICATION FOR U.S. PATENT 5,616,599

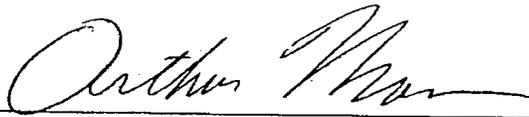
I, Daiichi Sankyo, Inc. ("Daiichi Sankyo"), certify that U.S. Patent No. 5,616,599 will not be infringed by the manufacture, use or sale of AZOR™ for

which this application is submitted, because Daiichi Sankyo has been granted a patent license by Sankyo Co., Ltd. (the owner of the patent). Enclosed with this certification is a letter from Sankyo confirming that it has a license agreement with Daiichi Sankyo and consents to an immediate effective date upon approval of this 505(b)(2) application (NDA 22-100).

PARAGRAPH IV CERTIFICATION FOR U.S. PATENT 6,878,703

I, Daiichi Sankyo, Inc. ("Daiichi Sankyo"), certify that U.S. Patent No. 6,878,703 will not be infringed by the manufacture, use or sale of AZOR™ for which this application is submitted, because Daiichi Sankyo has been granted a patent license by Sankyo Co., Ltd. (the owner of the patent). Enclosed with this certification is a letter from Sankyo confirming that it has a license agreement with Daiichi Sankyo and consents to an immediate effective date upon approval of this 505(b)(2) application (NDA 22-100).

Date: 1/31/07



Arthur Mann
Senior Director of Intellectual Property
Daiichi Sankyo, Inc.



SANKYO CO., LTD.
LICENSING DEPARTMENT
3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426
Japan



January 31, 2007

Norman Stockbridge, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 22-100
AZOR™ (proposed)
(amlodipine besylate and olmesartan medoxomil) Tablets

Dear Dr. Stockbridge:

Sankyo Co., Ltd. ("Sankyo") is submitting this letter at the request of our subsidiary, Daiichi Sankyo, Inc. ("Daiichi Sankyo"), the applicant for NDA 22-100 (amlodipine besylate/olmesartan medoxomil tablets).

Daiichi Sankyo is the holder of NDA 21-286 (Benicar® (olmesartan medoxomil)) and NDA 21-532 (Benicar HCT® (olmesartan medoxomil/hydrochlorothiazide)). Sankyo is the owner of U.S. Patent Nos. 5,616,599 and 6,878,703, which are listed in the Orange Book for each of those approved NDAs.

Sankyo has a licensing agreement with Daiichi Sankyo granting Daiichi Sankyo a license under those patents, and giving Daiichi Sankyo the right to market olmesartan medoxomil as a combination drug with amlodipine besylate. Sankyo consents to an immediate effective date of approval of Daiichi Sankyo's NDA 22-100.

Very truly yours,

A handwritten signature in cursive script that reads 'Richard B. Van Duyne'.

Richard B. Van Duyne
Head of Global Business Development
Sankyo Company, Ltd.

EXCLUSIVITY SUMMARY

NDA # 22-100

SUPPL #

HFD # 110

Trade Name AZOR

Generic Name amlodipine besylate and olmesartan medoxomil

Applicant Name Daiichi Sankyo Pharma Development

Approval Date, If Known Sep07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

This is a fixed-dose combination product of two approved drug products, amlodipine besylate and olmesartan medoxomil. This supplement required the review of clinical data to support the proposed indications of:

1. AZOR is indicated either alone or in combination with other antihypertensive

agents for the treatment of hypertension.

2. AZOR is indicated for initial therapy in patients with hypertension requiring a blood pressure reduction

b(4)

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 19-787	Norvasc (amlodipine besylate) Tablets
NDA# 21-286	Benicar (olmesartan medoxomil) Tablets
NDA# 21-532	Benicar HCT (olmesartan medoxomil/ hydrochlorothiazide) Tablets

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:

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(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:

The pivotal study was based on Sankyo protocol CS8663-A-U301,(Period II) titled "A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil plus Amlodipine Compared to Monotherapy in Patients with Mild to Severe Hypertension."

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"):

The pivotal study was based on Sankyo protocol CS8663-A-U301,(Period II) titled "A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil plus Amlodipine Compared to Monotherapy in Patients with Mild to Severe Hypertension."

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 # 70,410 YES ! NO
! Explain:

Investigation #2 !

IND #

YES

!
!
! NO
! Explain:

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

Investigation #1

YES

Explain:

!
!
! NO
! Explain:

Investigation #2

YES

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: Denise M. Hinton

Title: Regulatory Health Project Manager, Division of Cardiovascular and Renal Products

Date: 21Sep07

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

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

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/s/

Norman Stockbridge
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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA# : 22-100 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: November 27, 2006 PDUFA Goal Date: September 27, 2007

HFD -110 Trade and generic names/dosage form: AZOR (amlodipine besylate and olmesartan medoxomil) Tablets

Applicant: Daiichi Sankyo Pharma Development Therapeutic Class: Antihypertensive

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of hypertension

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: Pediatric data is available for amlodipine besylate and there is an ongoing pediatric program for olmesartan.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA ~~##-###~~

Page 3

This page was completed by: Denise M. Hinton

{See appended electronic signature page}

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

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/s/

Denise Hinton

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Request for Waiver of Pediatric Studies

Daiichi Sankyo, Inc. ("applicant") provides reference to 21 CFR 314.55(c) (2) for the purpose of requesting a full waiver of submitting assessments of pediatric safety and effectiveness for CS-8663 (olmesartan medoxomil and amlodipine besylate) tablets for the treatment of hypertension.

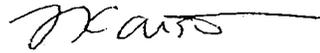
Reference is also made to the applicant's submission to IND 70,410, dated December 13, 2004, re: "Modification of Sankyo Pharma Briefing Document for FDA Meeting on December 20, 2004". Included therein is the pediatric study waiver request submitted to the Agency. The justification for full waiver is based on i) a pediatric clinical program is currently ongoing for olmesartan medoximil based on discussions and agreements with FDA, ii) pediatric studies have been conducted with amlodipine besylate and the results are included in the current US package insert for Norvasc® (amlodipine besylate), and iii) study of this fixed dose combination drug product in a pediatric population is unlikely to add substantial new information about the safety and efficacy beyond that captured in the individual component programs.

During the Type C guidance meeting on December 20, 2004, the Agency indicated that a pediatric study waiver would be granted for CS-8663 (olmesartan medoximil and amlodipine besylate). This agreement to grant a full waiver was confirmed during the Type B Pre-NDA meeting held on September 13, 2006. Applicant believes that the claim for full waiver is therefore supported by the Agency's agreement.

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Debarment Certification

On behalf of Daiichi Sankyo, Inc., I hereby certify that we did not and will not use in any capacity the services of any individual, partnership, corporation, or associations debarred under sub-sections (a) or (b) of Section 306 of the Federal Food, Drug, & Cosmetic Act in connection with NDA 022100 for olmesartan medoxomil/amlodipine besylate tablets.



Tetsuya Kaiso
Manager, Regulatory Affairs

8/22/2006

Date

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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	See attached list	

- (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 Tetsuya Kaiso	TITLE Manager, Regulatory Affairs
FIRM / ORGANIZATION Daiichi Sankyo, Inc	
SIGNATURE 	DATE 8/15/2006

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
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-100
Daiichi Sankyo, Inc.
Attention: Mr. Tetsuya (Ted) Kaiso
Manager, Regulatory Affairs
399 Thornall Street, 11th Floor
Edison, NJ 08837

Dear Mr. Kaiso:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AZOR (amlodipine and olmesartan medoxomil) 5/20, 5/40, 10/20 and 10/40 mg Tablets. We also refer to your May 22, 2007 submission, requesting feedback on the proposed Tables of Contents of Integrated Summary of Efficacy and Safety to support labeling for first-line use of AZOR.

We have reviewed the referenced material and have the following comment.

- With respect to your proposed table for clinical efficacy, please address the sensitivity of your analyses to the sparse data at the margins of observed baseline blood pressure in one of the following sections: 3.2.4, 3.2.5, 3.3, 3.3.1, 3.3.1.1, 3.3.1.2, 3.3.2, or 3.3.2.1.

If you have any questions, please call Alisea Crowley, Regulatory Health Project Manager, at (301) 796-1144.

Sincerely,

{See appended electronic signature page}

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

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this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
6/5/2008 05:07:19 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-100

Daiichi-Sankyo
Attention: Mr. Tetsuya Kaiso
399 Thornall Street
Edison, NJ 08837

Dear Mr. Kaiso:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and the meeting request dated February 15, 2008 for Azor™ (amlodipine besylate and olmesartan medoxomil) 5/20, 5/40, 10/20 and 10/40 mg Tablets.

We also refer to your meeting package dated February 15, 2008, containing the background information for the Type C meeting. Please review the attached meeting minutes from our April 3, 2008 discussion.

If you have any questions, please call:

Alisea Crowley, PharmD
Regulatory Health Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

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

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Meeting Minutes

Application Number: NDA 22-100

Sponsor: Daiichi-Sankyo
Drug: Azor™ (amlodipine besylate and olmesartan medoxomil)
5/20, 5/40, 10/20 and 10/40 mg Tablets

Type of Meeting: Guidance, Teleconference
Classification: Type C
Meeting Request Date: February 15, 2008
Confirmation Date: February 29, 2008

Meeting Date: April 3, 2008

Briefing Package Received: February 15, 2008
Preliminary Responses Sent: March 13, 2008

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Recorder: Alisea Crowley, Pharm.D.

ATTENDEES:

FDA

Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D., Deputy Director
Abraham Karkowsky, M.D., Team Leader, Medical Officer
Akinwale Williams, M.D., Medical Officer
Steven Bai, Ph.D., Statistician
Jialu Zhang, Ph.D., Statistician
Alisea Crowley, Regulatory Health Project Manager

Daiichi-Sankyo

Howard Hoffman, M.D., Vice President, US/EU & Regional Regulatory Affairs
Rich Cuprys, Executive Director, Regulatory Affairs
Tetsuya Kaiso, Manager, Regulatory Affairs
Reinilde Heyrman, M.D., Executive Director, Clinical Development
Michael Melino, Ph.D., Director, Clinical Development
Antonia Wang, Ph.D., Executive Director, Biostatistics
James Lee, Ph.D., Senior Staff Biostatistician, Biostatistics
Jane Li, M.D., Senior Director, Risk Management
Andy Li, Director, Global Project Management

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Background:

AZOR™ (amlodipine besylate and olmesartan medoxomil) was approved on September 26, 2007 for the treatment of hypertension, alone or with other antihypertensive agents. The sponsor requested a meeting with the Division to reach a consensus on the preliminary approach to support approval of AZOR™ for the treatment of hypertension in patients not adequately controlled with monotherapy and as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

Meeting (Power Point slides attached)

After introductions, Dr. Stockbridge stated that considering the constraints that exist with their data, the Sponsor's proposals are reasonable. He stated that the Division could not comment on the adequacy of the data for first-line treatment until after it has been reviewed. Dr. Stockbridge confirmed that the Sponsor's model seemed sufficient.

1.1 Lack of all approved dose strengths of amlodipine incorporated into the AZOR™ dose strengths:

Does the Division agree with this approach?

FDA Preliminary Response: Since we cannot compel you to market any particular strength, we will deal with the lack of certain doses by excluding populations who should be treated with these doses. For example the elderly should be started on a 2.5-mg dose of amlodipine. If this dose is not available, we would so note in the package insert.

Meeting: No further discussion during the teleconference.

1.2. Inadequate safety data on elderly populations: ages > 65 years or > 75 years

By including information on patients participating in add-on studies (CS8663-A-E302, CS8663-A-E303), which were not previously submitted, the sponsor will provide additional data on elderly patients.

Does the Division agree with this approach?

FDA Preliminary Response: Having additional information may not be sufficient. Since the elderly are more prone to hypotensive episodes, we do not see how a small observational study not specifically geared to assess hypotension would allay any concerns regarding the use of a combination product in the elderly. We would be willing to discuss the information that would be sufficient to include elderly within the initial therapy population.

Meeting: The Sponsor requested for the Division to elaborate on the preliminary comment "information that would be sufficient to include elderly within the initial therapy population." Dr. Stockbridge responded that the labeling description for the elderly population will reflect the data submitted for a particular elderly age group and it may describe limitations for that age group if the numbers are less than expected. Dr. Stockbridge agreed that no additional information would be needed for the evaluation of safety in the elderly.

1.3. Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients.

FDA Preliminary Response: Yes

Meeting: No further discussion during the teleconference.

1.4. There is a need for additional data from enriched populations; including the elderly particularly those with certain co-morbidities (diabetes, coronary artery disease, kidney disease and congestive heart failure).

By including information on patients participating in add-on studies (CS8663-A-E302 and CS8663-A-E303), the sponsor will provide additional data on elderly patients with co-morbidities such as diabetes, coronary artery disease, congestive heart failure, and kidney disease.

Does the Division agree with this approach?

FDA Preliminary Response: The approach seems reasonable; however, each of the above subpopulations has safety or efficacy issues that may or may not be addressed by a broad population-based study. For example, for diabetics, we would be interested in glucose control. The adequacy of the observational database to allow the use of drug as initial therapy in each of these subpopulations would depend on the nature of what signal of concern could be ruled out.

Meeting: The Sponsor asked what the Division would recognize as a signal of concern for each of the subpopulations in addition to the proposed adverse events (AE's) of interest. The Division responded that exposure is not enough and it is critical to determine that vulnerable systems are not affected. In addition to the proposed AE's, the Division recommended:

- 1) Adding the categories of diabetic control (e.g., hyperglycemia and hypoglycemia), falls and fractures to the list of "AE's of Interest" for assessment of the elderly with co-morbidities
- 2) Combine states which describe renal dysfunction (e.g. kidney disease should include dysuria, anuria & oliguria)

The Sponsor asked whether specific efficacy analyses will be needed in these subpopulations due to the small number per group. The Division replied that risk and benefit assessment is needed in these subpopulations even if there are small numbers per group. It was agreed that summary statistics of efficacy would be sufficient without formal analyses.

1.5. The NDA review showed several laboratory abnormalities that are statistically significant in the mean change from baseline to end of week 8 particularly among patients exposed to AZOR™. Some of these include elevated liver enzymes and platelets as well as decreased hemoglobin and hematocrit. For initial therapy the risk to benefit should be justified.

The sponsor will analyze the observed changes and provide an adequate risk benefit rationale.

Does the Division agree with this approach?

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FDA Preliminary Response: In general, we think that assessment of lab values may be acceptable.

Meeting: No further discussion during the teleconference.

2. EFFICACY DATA

The sponsor will provide efficacy data according to the guidance provided in the document "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs". In addition, the sponsor intends to repeat in the submission the information that was included in the original NDA 22-100 in support for a first line indication.

Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting: No further discussion during the teleconference.

3. Adequacy of proposed information for submission to obtain label for initial therapy of AZOR™ in hypertensive patients.

For this sNDA, the Sponsor will present efficacy data on AZOR™ in hypertensive patients in the requested format and additional safety data in subpopulations as requested by the Division and described in this document.

Are any other efficacy or safety data required to support an indication for AZOR™ for initial therapy in hypertensive patients?

FDA Preliminary Response: Several of the preceding responses outlined the specific concerns for certain populations.

Meeting: No further discussion during the teleconference.

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AZOR™ (NDA 22-100)

Discussion on Initial Therapy

April 3, 2008

Objectives for April 3 Meeting

- a) Obtain agreement on the preliminary approach to support registration
- b) Discuss the methodology used for subgroup analysis, and the presentation of safety and efficacy data in the NDA
 - 1) Elderly populations
 - 2) Severe hypertension
 - 3) Patients with renal impairment
 - 4) Elderly with certain co-morbidities

page 3



Background Information

1. Regulatory history

- a) September 21 2007 - During labeling negotiations for AZOR™, FDA indicated that the initial therapy indication would not likely require additional studies.
- b) September 26, 2007 - FDA letter deferred a decision on first-line use of AZOR™ and included considerations how to address the areas of concern.
- c) November 20, 2007 - FDA document "Points to Consider In Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs"

2. Proposed indication for initial therapy

AZOR™ is indicated for the treatment of hypertension in patients likely to need multiple drugs to achieve their blood pressure goals.

page 1



Sponsor Updates to FDA Responses

1. Questions to the FDA letter dated 9/26/2007

- 1.1 Lack of a) approved dose strengths of amlodipine incorporated into the AZOR™ dose strengths – Agree
- 1.2 Inadequate safety data on elderly populations: ages > 65 years or > 75 years – To be discussed
- 1.3 Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients
 - (a) Severe hypertension – To be discussed
 - (b) Patients with renal impairment – To be discussed
 - (c) Patients with hepatic impairment – Agree

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Sponsor Updates to FDA Responses

1. Questions to the FDA letter dated 9/26/2007 (continued)

1.4 Additional data from enriched populations: including the elderly particularly those with certain co-morbidities (diabetes, coronary artery disease, kidney disease and congestive heart failure) – To be discussed

1.5 Risk to benefit justification for several laboratory abnormalities – Agree

2. Efficacy data – Agree

3. Adequacy of proposed information for submission to obtain label for initial therapy of AZOR™ in hypertensive patient – Agree

page 1



1.2. Inadequate safety data on elderly populations: ages , 65 years or , 75 years

• Daiichi Sankyo Question

- By including information on patients participating in add-on studies (CS8663-A-E302, CS8663-A-E303), which were not previously submitted, the sponsor will provide additional data on elderly patients. Does the Division agree with this approach?

• FDA Preliminary Response

- Having additional information may not be sufficient. Since the elderly are more prone to hypotensive episodes, we do not see how a small observational study not specifically geared to assess hypotension would allay any concerns regarding the use of a combination product in the elderly. We would be willing to discuss the information that would be sufficient to include elderly within the initial therapy population.

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1.2. Inadequate safety data on elderly populations: ages .65 years or .75 years

- Daiichi Sankyo Points for Clarification
 - a) What additional information would be "sufficient to include elderly within the initial therapy population"? (please see the preliminary analysis data in the tables 1-1 to 1-7 in the backup slides behind)
 - b) The sponsor would also like to clarify the FDA definition of elderly (.65 years or .75 years?)

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1.3 Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients
(a) Severe hypertension

- Daiichi Sankyo Question
 - Does the Division agree that, by including the exposure data on severely hypertensive patients, adequate information will be delivered to analyze a first line indication of Azor™?
- FDA Preliminary Response
 - The approach seems reasonable. However, the claim can only extend over the range of blood pressures available to show effects of the combination and components and for whom the safety data appear to be commensurate with those effects.

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1.3 Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients
(a) Severe hypertension

- Daiichi Sankyo Points for Clarification
 - a) Efficacy

The sponsor will be providing the efficacy analysis based on the FDA guidance "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs" (Nov. 23, 2007), in which FDA does not make a distinction between severe and non-severe hypertensive patients to evaluate the effect of the drug on BP (please see the figures 2-1 & 2-2 in the backup slides behind). Is this approach acceptable for evaluation of efficacy?
 - b) Safety

Concerning safety evaluation, the sponsor would like clarification of the FDA preliminary response "the claim can only extend over the range of blood pressures for whom the safety data appear to be commensurate with those effects" (please see the preliminary analysis data in the tables 3-1 to 3-4 in the backup slides behind)

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1.3 Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients
(b) Patients with renal impairment

- Daiichi Sankyo Question
 - Does the Division agree that, by including the exposure data on renal impaired patients, adequate information will be delivered to analyze a first line indication of Azor™?
- FDA Preliminary Response
 - We will need to review safety data in the cohort with renal impairment.

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1.3 Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients
(b) Patients with renal impairment

- Daiichi Sankyo Points for Clarification
 - To define renal impairment, the sponsor will use a calculated creatinine clearance of < 60 ml/min as cut-off. This calculation will be based on the creatinine measurement obtained at baseline.
 - By including these safety data, information on 133 subjects with renal impairment exposed to CS-8663 during the double-blind periods of the studies will be available for review.
 - To define renal impairment, is this calculation of creatinine clearance acceptable?

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1.4. Additional data from enriched populations; including the elderly particularly those with certain co-morbidities (diabetes, coronary artery disease, kidney disease and congestive heart failure

- Daiichi Sankyo Question
 - By including information on patients participating in add-on studies (CS8663-A-E302 and CS8663-A-E303), the sponsor will provide additional data on elderly patients with co-morbidities such as diabetes, coronary artery disease, congestive heart failure, and kidney disease. Does the Division agree with this approach?
- FDA Preliminary Response
 - The approach seems reasonable; however, each of the above subpopulations has safety or efficacy issues that may or may not be addressed by a broad population-based study. For example, for diabetes we would be interested in glucose control. The adequacy of the observational database to allow the use of drug as initial therapy in each of these subpopulations would depend on the nature of what signal of concern could be ruled out.

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Table 1-3 Overview of AE's by Combined Treatment Group in Patients ≥85 yrs old Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n= 23)	Combination Treatment (n= 23)	Subcutaneous Insulin (n= 23)	Subcutaneous Insulin + Metformin (n= 23)	Total (n= 92)
Very Serious Adverse Events (VSAE) (1)					
All AE	11 (47.8)	12 (52.1)	12 (52.1)	12 (52.1)	26 (28.2)
Serious AE	8 (34.8)	11 (47.8)	11 (47.8)	11 (47.8)	20 (21.7)
AEs by System					
All AE	11 (47.8)	12 (52.1)	12 (52.1)	12 (52.1)	26 (28.2)
GI	7 (30.4)	11 (47.8)	11 (47.8)	11 (47.8)	19 (20.6)
Respiratory	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	2 (2.2)
Musculoskeletal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neurological	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infectious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All-cause mortality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs that caused discontinuation during treatment					
All AE	7 (30.4)	12 (52.1)	12 (52.1)	12 (52.1)	26 (28.2)
Serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1-4 Overview of AE's by Combined Treatment Group in Patients ≥75 yrs old Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n= 30)	Combination Treatment (n= 30)	Subcutaneous Insulin (n= 30)	Subcutaneous Insulin + Metformin (n= 30)	Total (n= 120)
Very Serious Adverse Events (VSAE) (1)					
All AE	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	4 (3.3)
Serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs by System					
All AE	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	4 (3.3)
GI	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	4 (3.3)
Respiratory	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neurological	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infectious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All-cause mortality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs that caused discontinuation during treatment					
All AE	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	4 (3.3)
Serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1-5 Number(%) of Patients with Treatment-Emergent AE's in AE Categories of Interest By Combined Treatment Group in Patients ≥85 yrs old Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n= 23)	Combination Treatment (n= 23)	Subcutaneous Insulin (n= 23)	Subcutaneous Insulin + Metformin (n= 23)	Total (n= 92)
Cough	11 (47.8)	12 (52.1)	12 (52.1)	12 (52.1)	26 (28.2)
Dyspnea	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	4 (4.3)
Headache	11 (47.8)	12 (52.1)	12 (52.1)	12 (52.1)	26 (28.2)
Diarrhea and Nausea	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	4 (4.3)
Constipation	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	4 (4.3)
Abdominal Pain	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	4 (4.3)
Flatulence	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	4 (4.3)

Table 1-6 Number(%) of Patients with Treatment-Emergent AE's in AE Categories of Interest By Combined Treatment Group in Patients ≥75 yrs old Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n= 30)	Combination Treatment (n= 30)	Subcutaneous Insulin (n= 30)	Subcutaneous Insulin + Metformin (n= 30)	Total (n= 120)
Cough	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	4 (3.3)
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	4 (3.3)
Diarrhea and Nausea	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	4 (3.3)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1-7 Number(%) of Patients with Treatment-Emergent AE's in AE Categories of Interest By Combined Treatment Group in Patients ≥75 yrs old Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n= 30)	Combination Treatment (n= 30)	Subcutaneous Insulin (n= 30)	Subcutaneous Insulin + Metformin (n= 30)	Total (n= 120)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea and Nausea	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Figure 2-1 Efficacy analysis: likelihood to achieve SBP < 140 mmHg

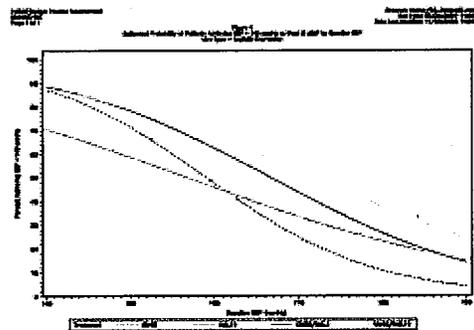
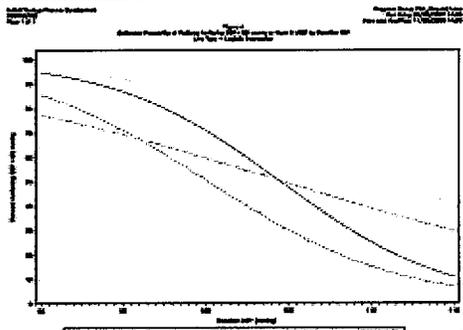


Figure 2-2 Efficacy analysis: likelihood to achieve DBP < 90 mmHg



Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients
 (a) Severe hypertension

- The Safety Tables will include (preliminary analysis data are presented):
 - Overview of AE's by combined treatment group (placebo, monotherapy, and combination therapy) for patients with severe HTN (>180/110)
 - Number of patients with treatment-emergent AE's of particular interest by combined treatment group for patients with severe HTN.
 - AE's of particular interest include: hypotension, dizziness, & vertigo, syncope, edema, headache, hyperkalemia, renal-related AE and hepatic-related AE.

Table 3-1 Overview of AE's by Combined Treatment Group in Patients with Severe HTN (>180/110) Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n=101)	Amlodipine (n=101)	Losartan (n=101)	Amlodipine/Losartan (n=101)	Total (n=404)
TRT-emergent adverse events (n=34)					
All AE	11 (10.9)	13 (12.9)	11 (10.9)	13 (12.9)	38 (9.4)
Serious AE	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
TRT-related adverse events (n=10)					
All AE	4 (3.9)	4 (3.9)	4 (3.9)	4 (3.9)	16 (4.0)
Serious AE	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
TRT-related adverse events (n=10)					
All AE	4 (3.9)	4 (3.9)	4 (3.9)	4 (3.9)	16 (4.0)
Serious AE	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
All non-related adverse events (n=24)					
All AE	11 (10.9)	13 (12.9)	11 (10.9)	13 (12.9)	48 (11.9)
Serious AE	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)

Table 3-2 Overview of AE's by Combined Treatment Group in Patients with Non-Severe HTN Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n=101)	Amlodipine (n=101)	Losartan (n=101)	Amlodipine/Losartan (n=101)	Total (n=404)
TRT-emergent adverse events (n=34)					
All AE	11 (10.9)	13 (12.9)	11 (10.9)	13 (12.9)	38 (9.4)
Serious AE	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
TRT-related adverse events (n=10)					
All AE	4 (3.9)	4 (3.9)	4 (3.9)	4 (3.9)	16 (4.0)
Serious AE	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
TRT-related adverse events (n=10)					
All AE	4 (3.9)	4 (3.9)	4 (3.9)	4 (3.9)	16 (4.0)
Serious AE	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
All non-related adverse events (n=24)					
All AE	11 (10.9)	13 (12.9)	11 (10.9)	13 (12.9)	48 (11.9)
Serious AE	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)

Table 3-3 Number(%) of Patients with Treatment-Emergent AE's in AE Categories of Interest by Combined Treatment Group in Patients with Severe HTN (>180/110) Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n=101)	Amlodipine (n=101)	Losartan (n=101)	Amlodipine/Losartan (n=101)	Total (n=404)
Dizziness	2 (2.0)	2 (2.0)	1 (1.0)	4 (4.0)	9 (2.2)
Hypotension	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	2 (0.5)
Headache	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
TRT-emergent hypotension	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (1.0)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TRT-related hypotension	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	2 (0.5)
Hyperkalemia	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	3 (0.7)
Hyperkalemia	0 (0.0)	1 (1.0)	1 (1.0)	1 (1.0)	3 (0.7)

Table 3-4 Number(%) of Patients with Treatment-Emergent AE's in AE Categories of Interest by Combined Treatment Group in Patients with Non-Severe HTN Phase III Double-Blind Cohort (preliminary data)

Adverse Event Category	Placebo (n=101)	Amlodipine (n=101)	Losartan (n=101)	Amlodipine/Losartan (n=101)	Total (n=404)
Dizziness	11 (10.9)	13 (12.9)	11 (10.9)	13 (12.9)	48 (11.9)
Hypotension	0 (0.0)	1 (1.0)	1 (1.0)	1 (1.0)	3 (0.7)
Headache	11 (10.9)	13 (12.9)	11 (10.9)	13 (12.9)	48 (11.9)
Dizziness and Vertigo	7 (6.9)	11 (10.9)	10 (9.9)	10 (9.9)	38 (9.4)
Syncope	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	2 (0.5)
TRT-emergent hypotension	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	2 (0.5)
Hyperkalemia	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	3 (0.7)
Hyperkalemia	0 (0.0)	1 (1.0)	1 (1.0)	1 (1.0)	3 (0.7)

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Definitions used in the tables:

Treatment-emergent adverse events (AE) that has a start date on or after the first dose of randomized study medication.

Percentage is calculated using number of patients in the column heading as denominator.

Although a patient may have had two or more TEAEs, the patient is counted only once within a category. The same patient may appear in different categories.

Drug-related is defined as definitely, possibly, or probably related to randomized study medication.

Edema includes MedDRA Preferred Terms of Edema peripheral, Cerebral, Pitting edema, Generalized edema, and Localized edema.

Hypotension includes MedDRA Preferred Terms of Hypotension and Orthostatic hypotension.

Dizziness includes MedDRA Preferred Terms of Dizziness and Dizziness postural.

Renal Related includes MedDRA Preferred Terms of Blood urea nitrogen increased, Blood creatinine increased, and Renal impairment.

Hepatic Related includes MedDRA Preferred Terms of Alanine aminotransferase increased, Aspartate aminotransferase increased, Bilirubin total increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, and Liver function test abnormal.

Torsionades includes MedDRA Preferred Terms of Torsionades pointes and Torsionades pointes.

Hypertension includes MedDRA Preferred Terms of Hypertension, Blood pressure increased, and Hypertension.



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/s/

Norman Stockbridge
4/28/2008 11:14:52 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-100

Daiichi-Sankyo
Attention: Ms. Tetsuya Kaiso
399 Thornall Street
Edison, NJ 08837

Dear Ms. Kaiso:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and the meeting package dated February 15, 2008 for Azor™ (amlodipine besylate and olmesartan medoxomil) 5/20, 5/40, 10/20 and 10/40 mg Tablets.

We have completed the review of your submission and have the following preliminary comments.

"This material consists of our preliminary responses to your questions and any additional comments in preparation for the teleconference scheduled for April 3, 2008 from 2:30-3:30 pm between Daiichi-Sankyo and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to 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 the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principle questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan, the purpose of the meeting, and/or to the questions] (based on our responses herein), we may not be able to reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. 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 to discuss the possibility of including these for discussion at the meeting."

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1.1 Lack of all approved dose strengths of amlodipine incorporated into the AZOR™ dose strengths:

Does the Division agree with this approach?

FDA Preliminary Response: Since we cannot compel you to market any particular strength, we will deal with the lack of certain doses by excluding populations who should be treated with these doses. For example the elderly should be started on a 2.5-mg dose of amlodipine. If this dose is not available, we would so note in the package insert.

**1.2. Inadequate safety data on elderly populations: ages > 65 years or > 75 years
By including information on patients participating in add-on studies (CS8663-A-E302, CS8663-A-E303), which were not previously submitted, the sponsor will provide additional data on elderly patients.**

Does the Division agree with this approach?

FDA Preliminary Response: Having additional information may not be sufficient. Since the elderly are more prone to hypotensive episodes, we do not see how a small observational study not specifically geared to assess hypotension would allay any concerns regarding the use of a combination product in the elderly. We would be willing to discuss the information that would be sufficient to include elderly within the initial therapy population.

1.3. Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients.

By including information on patients participating in add-on studies (CS8663-A-E302, CS8663-A-E303), the sponsor will provide more exposure data on severely hypertensive patients and patients with renal impairment. The sponsor proposes that initial therapy with AZOR™ for hepatic impairments is not recommended, as those were not specifically studied during the program.

Does the Division agree with this approach?

(a) Severe hypertension

Does the Division agree that, by including the exposure data on severely hypertensive patients, adequate information will be delivered to analyze a first line indication of Azor™?

FDA Preliminary Response: The approach seems reasonable. However, the claim can only extend over the range of blood pressures available to show effects of the combination and components and for whom the safety data appear to be commensurate with those effects.

(b) Patients with renal impairment

Does the Division agree that, by including the exposure data on renal impaired patients, adequate information will be delivered to analyze a first line indication of Azor™?

FDA Preliminary Response: We will need to review safety data in the cohort with renal impairment.

(c) Patients with hepatic impairment

Does the Division agree that initial therapy with AZOR™ for hepatic impairments is not recommended?

FDA Preliminary Response: Yes

1.4. There is a need for additional data from enriched populations; including the elderly particularly those with certain co-morbidities (diabetes, coronary artery disease, kidney disease and congestive heart failure).

By including information on patients participating in add-on studies (CS8663-A-E302 and CS8663-A-E303), the sponsor will provide additional data on elderly patients with co-morbidities such as diabetes, coronary artery disease, congestive heart failure, and kidney disease.

Does the Division agree with this approach?

FDA Preliminary Response: The approach seems reasonable; however, each of the above subpopulations has safety or efficacy issues that may or may not be addressed by a broad population-based study. For example, for diabetics, we would be interested in glucose control. The adequacy of the observational database to allow the use of drug as initial therapy in each of these subpopulations would depend on the nature of what signal of concern could be ruled out.

1.5. The NDA review showed several laboratory abnormalities that are statistically significant in the mean change from baseline to end of week 8 particularly among patients exposed to AZOR™. Some of these include elevated liver enzymes and platelets as well as decreased hemoglobin and hematocrit. For initial therapy the risk to benefit should be justified.

The sponsor will analyze the observed changes and provide an adequate risk benefit rationale.

Does the Division agree with this approach?

FDA Preliminary Response: In general, we think that assessment of lab values may be acceptable.

2. EFFICACY DATA

The sponsor will provide efficacy data according to the guidance provided in the document "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs". In addition, the sponsor intends to repeat in the submission the information that was included in the original NDA 22-100 in support for a first line indication.

Does the Division agree with this approach?

FDA Preliminary Response: Yes.

3. Adequacy of proposed information for submission to obtain label for initial therapy of AZOR™ in hypertensive patients.

For this sNDA, the Sponsor will present efficacy data on AZOR™ in hypertensive patients in the requested format and additional safety data in subpopulations as requested by the Division and described in this document.

Are any other efficacy or safety data required to support an indication for AZOR™ for initial therapy in hypertensive patients?

FDA Preliminary Response: Several of the preceding responses outlined the specific concerns for certain populations.

If you have any questions, please call:

Alisea Crowley, Pharm.D.
Regulatory Health Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

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

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Norman Stockbridge
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NDA 22-100
AZOR Tablets
(amlodipine and olmesartan medoxomil)
Page 1

RHPM Overview

Application: NDA 22-100
AZOR (amlodipine and olmesartan medoxomil) Tablets
5/20, 5/40, 10/20 and 10/40 mg

Sponsor: Daiichi-Sankyo Pharma Development
Classification: Standard
Submission Date: November 26, 2006
Receipt Date: November 27, 2006
User Fee Goal Date: September 27, 2007

Background

This NDA was submitted electronically in eCTD format. This application provides information for the review of a fixed-dose combination tablet, AZOR (amlodipine and olmesartan medoxomil), for the treatment of hypertension, alone or with other antihypertensive agents.

Amlodipine besylate is a calcium channel blocker and is approved for the treatment of hypertension (NDA 19-787/ Norvasc). Olmesartan medoxomil is an angiotensin II antagonist approved for the treatment of hypertension (NDA 21-286/ Benicar and NDA 21-532/ Benicar HCT (olmesartan and medoxomil/hydrochlorothiazide)).

The sponsor requests approval of this application for the two indications of:

1. AZOR is indicated either alone or in combination with other antihypertensive agents for the treatment of hypertension.
2. AZOR is indicated for initial therapy in selected patients with hypertension

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This NDA was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and contains full reports of safety and effectiveness of the combination drug. Reference is made to certain information previously submitted to the Agency for Norvasc (amlodipine besylate) Tablets. Paragraph II and III patent certifications regarding the two patents listed by Pfizer in the Orange Book for Norvasc are included in the application.

Secondary Medical Review

In his August 29, 2007 review, Dr. Karkowsky supports the approvability of the fixed-dose combination product, AZOR (amlodipine and olmesartan medoxomil) for the treatment of hypertension. His memo states that the combination at dose of OM from 10- to 40- mg and AML at doses of 5- or 10- mg is clearly superior to the individual components in decreasing both systolic and diastolic blood pressure. Approval of the

second indication may be addressed after the sponsor addresses the specifics as to how to represent the currently available data in the labeling.

Primary Medical Review

In his review dated, August 9, 2007, Dr. Williams recommends approval for the first indication. He supports AZOR being indicated either alone or in combination with other antihypertensive agents for the treatment of hypertension, as the pivotal study demonstrated statistically significant lowering of seated diastolic and systolic blood pressure compared to the corresponding monotherapy components. However, he does not recommend approval for the indication for initial therapy i

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based on lack of adequate safety data in selected populations (i.e., elderly, inadequate exposure of severely hypertensive, renal or hepatic impaired patients).

Statistical Review

In his review dated July 2, 2007, Steven Bai wrote that the results from the double-blind treatment period of study CS8663-AU301 confirmed in the overall study population that olmesartan medoxomil 10 mg, 20 mg, or 40 mg given together with amlodipine 5 mg or 10 mg reduced both diastolic and systolic blood pressure to a greater extent than monotherapy with each of the component drugs that made up each combination. The combination of OM 40 mg + AML 10 mg resulted in the greatest mean reduction in SeDBP and SeSBP. The comparisons of the mean reductions in both SeDBP and SeSBP between the combination treatments and the individual monotherapy treatments were all highly statistically significant. Treatment goals were reached for a greater percentage of patients on the higher dose combinations. The combination treatments all reduced more blood pressure numerically than the individual monotherapy treatments in all of the subgroups analyzed.

Clinical Pharmacology Review

In her initial review dated July 26, 2007, Dr. Lydia Velazquez recommended that a waiver for performing additional bioequivalence studies with the intermediate strengths be denied unless the sponsor was compliant and submitted sufficient data to verify the calculations made and data in three different media.

The sponsor submitted the biowaiver information for the similarity testing of the 5/20, 10/20 and 5/40 mg intermediate strengths on August 15, 2007, which was subsequently reviewed and deemed acceptable. In her review dated September 5, 2007, Dr. Velazquez recommended that a waiver for performing additional bioequivalence studies with the intermediate strengths be granted.

Based upon the provided information, the following dissolution method is approved for this application.

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NDA 22-100
AZOR Tablets
(amlodipine and olmesartan medoxomil)
Page 3

Apparatus: USP 2
Media: 900 mL, phosphate buffer, pH 6.8 at 37° C
Speed: 50 RPM
Q value at 30 minutes: **b(4)** for olmesartan medoxomil
b(4) for amlodipine besylate

Pharmacology review

In his July 30, 2007 review, Dr. Jagadeesh recommended approval of the combination product from a pharmacology perspective and wrote that "Since these two classes of agents have different modes of action, their combination should provide an additive or synergistic antihypertensive effect when compared to single drug treatment."

In his review, he also noted that "The combined administration of amlodipine besylate and olmesartan medoxomil to rats did not augment any existing toxicities of the individual agents, nor induce any new toxicities and resulted in no toxicologically synergistic effects. However, a significant increase in systemic exposure to olmesartan (8.5-fold increase in AUC) was observed in the presence of amlodipine besylate. Mechanistic studies demonstrated that the observed increase in olmesartan exposure in the presence of amlodipine besylate is dependent on the dose of each drug in the combination and a change in the absorption of olmesartan medoxomil as a result of a marked relaxant effect of amlodipine on the intestinal smooth muscle. The highly pronounced systemic exposure to olmesartan, however, did not translate into unexpectedly toxic effects when compared to effects produced by olmesartan medoxomil alone. Furthermore, findings from human PK studies (report #CS8663-A-U101) demonstrated no interactions between the two drugs; mean olmesartan AUC values for groups receiving the combination (10/40 mg amlodipine/olmesartan medoxomil/day) or olmesartan medoxomil alone (40 mg/day) were, respectively, 6891 and 6794 ng.h/ml. Thus, it is concluded that the observed large increase in systemic exposure to olmesartan resulting from co-administration of amlodipine besylate in rats not a concern for humans when the combination is administered in accordance with the proposed labeling for this product.

Recommendations were made for labeling and incorporated into the final agreed upon labeling with minor revisions.

Chemistry review

Dr. Prafull Shiromani conducted three reviews dated August 9, September 6 and 18 2007. In the review dated September 18, 2007 Dr. Shiromani recommended approval of the combination product from a CMC perspective based on the receipt of the overall acceptable establishment report from Office of Compliance. All other CMC related issues documented in the reviews dated August 9 and September 6 have been resolved. The Sponsor has revised the labeling (Highlights, Package Insert and Carton and Container) according to the FDA recommendations as shown as an attachment to the approval letter.

Environmental Assessment

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

EES Report

The Office of Compliance provided an overall recommendation of "Acceptable" for the manufacturing sites inspected.

Division of Scientific Investigations

DSI audits were not requested. The individual components of the combination product are approved and the Division considered it unlikely that any unusual safety concerns would be detected by individual site reviews.

Pediatrics

The Sponsor requested a waiver of the pediatric requirement for the combination product based on the fact that pediatric data was available for amlodipine besylate and that there was an pediatric written request issued for olmesartan. During a Type C Guidance Meeting held on December 20, 2004, the Agency indicated that a waiver would be granted for the combination product based on the above and we do not usually require pediatric studies in fixed dose combination products. The Acknowledgement Letter, dated December 15, 2006 noted that a full waiver was granted.

Labeling

The original submission contains proposed draft labeling in SPL and PLR format for the package insert (PI) and container and carton labeling.

DDMAC provided comments on the proposed PI in a review dated April 30, 2007.

DMETS concluded that the proposed proprietary name "AZOR" was acceptable and provided additional comments on the proposed PI in their final review dated September 20, 2007 (The initial tradename review was completed on May 16, 2007).

The SEALD team provided feedback via marked-up labeling on August 29, 2007, which was also reviewed by Dr. Temple.

The sponsor revised the container and carton labeling and submitted it via email on September 5, 2007 and electronically to the EDR on September 13, 2007. It was found acceptable.

The agreed upon PI was sent to the sponsor on September 18, 2007. The Division communicated additional revisions to the PI via email on September 20, 21 (telecon and email), and 24 (telecon and email). Agreed-upon labeling was received via email on September 24, 2007 and is attached to the approval letter.

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NDA 22-100
AZOR Tablets
(amlodipine and olmesartan medoxomil)
Page 5

Pre-Approval Safety Conference

No Pre-Approval Safety Conference was held because there were no safety issues with this NDA as this is a 505(b)(2) application, with both components of the combination product already approved.

User Fee

The user fee for this application was paid in full (User Fee ID# PD3006796).

CSO Summary

The Immediate Office and Office of the Chief Counsel cleared this 505(b)(2) application for action on September 12, 2007.

An Approval letter based on agreed-upon labeling will be drafted for Dr. Stockbridge's signature. A General Correspondence letter will also be issued with regard to the steps necessary to be approved for the indication of first-line use.

Denise Hinton
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

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/s/

Denise Hinton

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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

9/26/07

NDA 22-100

Daiichi Sankyo, Inc.
Attention: Mr. Tetsuya Kaiso
399 Thornall Street
Edison, NJ 08837

Dear Mr. Kaiso:

Please refer to your New Drug Application (NDA) submitted on November 27, 2006 under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for AZOR (amlodipine and olmesartan medoxomil) 5/20, 5/40, 10/20, and 10/40 mg Tablets.

We acknowledge your interest in obtaining an indication for first-line use of AZOR in hypertension, but we are deferring a decision on this issue until the principles are better defined. As we prepare detailed specifications for the data analysis that will be needed to support labeling for first-line use, we ask you to consider how to address the following areas of concern:

- 1) Lack of all approved dose strengths of amlodipine incorporated into the AZOR dose strengths.
- 2) Inadequate safety data on elderly populations: ages > 65 years or > 75 years.
- 3) Inadequate exposure of certain specific subgroups, including severely hypertensive patients (> 180/110), renal or hepatic impaired patients.
- 4) There is a need for additional data from enriched populations; including the elderly particularly those with certain co-morbidities (diabetes, coronary artery disease, kidney disease and congestive heart failure).
- 5) The NDA review showed several laboratory abnormalities that are statistically significant in the mean change from baseline to end of week 8 particularly among patients exposed to AZOR. Some of these include elevated liver enzymes and platelets as well as decreased hemoglobin and hematocrit. For initial therapy the risk to benefit should be justified.

If you have any questions, please call Denise Hinton, Regulatory Health Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
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8/29/07

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	Friday, August 24, 2007
TIME:	1100 – 1130 ET
APPLICATION:	NDA 22-100
SPONSOR:	Daiichi Sankyo Pharma Development
DRUG NAME:	AZOR (amlodipine besylate/olmesartan medoxomil)
TYPE OF MEETING:	FDA Requested CMC
MEETING CHAIR:	Kasturi Srinivasachar, Ph.D., Pharmaceutical Assessment Lead
MEETING RECORDER:	Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

FDA PARTICIPANTS:

CENTER OF DRUG EVALUATION AND RESEARCH

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

EXTERNAL PARTICIPANTS:

Dale Adkisson, Senior Director, QA
 Paulette Kosmoski, Executive Director, US/EU & Regional Regulatory Affairs-CMC

BACKGROUND:

Daiichi Sankyo Pharma Development (Daiichi Sankyo) has submitted NDA 22-100 dated November 27, 2006, for AZOR (mg amlodipine besylate/ mg olmesartan medoxomil) 5/20, 5/40, 10/20, and 10/40 tablets. On June 29, 2007, FDA sent a CMC information request letter for additional information. Daiichi Sankyo submitted a response to FDA's CMC letter on August 2, 2007, (SN 011). A teleconference was held on Friday, August 24, 2007 at FDA's request, to discuss the post-approval stability bracketing and matrixing protocol design.

TELECONFERENCE:

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Drug Product Impurity Specifications Daiichi Sankyo requested comment regarding the drug product impurity specifications previously submitted to the NDA. FDA indicated that there was no feedback at this time, and that the review is continuing. FDA further indicated that no feedback would be provided if the review of the proposal is determined to be acceptable.

Dissolution Specifications Daiichi Sankyo requested comment regarding the 75 RPM and 50 RPM dissolution specifications previously submitted to the NDA. FDA indicated that the review is ongoing and that any comments will be provided in the action letter.

Labeling FDA requested an update regarding the submission of revised labeling. Daiichi Sankyo acknowledged the receipt of labeling comments from CMC and DMETS reviews, and would submit a revised label soon. Daiichi Sankyo acknowledged that the label would remove besylate from the amlodipine besylate established name.

The teleconference ended amicably.

CONCURRENCE:

Minutes Preparer:

{See appended electronic signature page}

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

Chair Concurrence:

{See appended electronic signature page}

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

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/s/

Scott Goldie
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PROJECT MANAGER FOR QUALITY

Kasturi Srinivasachar
8/27/2007 10:17:23 AM
CHEMIST



01/29/07

NDA 22-100

INFORMATION REQUEST LETTER

Daiichi Sankyo, Inc.
Attention: Paulette F. Kosmoski
Senior Director, Regulatory Affairs – CMC
399 Thornall Street, 11th Floor
Edison, NJ 08837

Dear Ms. Kosmoski:

Please refer to your November 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AZOR (amlodipine besylate and olmesartan medoxomil) 5/20, 5/40, 10/20, 10/40 mg tablets.

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

A deficiency letter has been sent to the DMF holder of olmesartan medoxomil – DMF #14,953. Ensure that the DMF holder responds to this letter in a timely fashion so as to facilitate review of this NDA.

1) S.3.2 Impurities:

There is a discrepancy in the test _____ between _____ Impurity Specification Table where a foot note states that _____ has requested exemption from routine testing of this solvent and the Specification Table in S.4.1 for amlodipine besylate which implies that _____ will be routinely tested. Confirm that _____ will be tested on every lot of the drug substance.

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2) S.4.3 Validation of Analytical Procedures:

Validate the following procedures for amlodipine besylate and provide the validation information:

- Potentiometric Titration assay procedure.
- Particle Size measurement.

We do not agree with your assertion that the above methods do not require validation.

3) P.2.3 Manufacturing Process Development

Provide the basis for your particle size acceptance criteria, _____ for olmesartan medoxomil drug substance.

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- 4) P.6 Reference Standards:
You have provided COAs of the known impurities
COAs on the additional known impurities – amlodipine impurity
- Provide
and
- 5) P.8.1 Stability Summary and Conclusion:
Based on evaluation of the 12 months stability data and the shelf life calculated for Total Impurities via statistical analysis, both presented in the NDA amendment, tighten its shelf life acceptance criterion. Exclude from the computation.
- 6) P.8.2 Post-approval Stability Protocol and Stability Commitment:
The first three commercial batches of the four marketed strengths should be tested in each container/closure system, unless appropriately bracketed, under long term and accelerated storage conditions. Thereafter, one batch of each strength in each container/closure system should be tested annually at long term storage condition. Accordingly, revise your protocol.
- 7) II Review of Common Technical Document – Quality (CtdQ) Module 1; A. Labeling and Packaging Insert:
The established name for amlodipine besylate does not match the labeled strength. Revise all labeling using the following format. As an example, for 5 mg/20 mg:

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If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

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

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/s/

Ramesh Sood
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-100

Daiichi Sankyo, Inc.
Attention: Mr. Tetsuya Kaiso
399 Thornall Street
Edison, NJ 08837

Dear Mr. Kaiso:

Please refer to your November 27, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AZOR (amlodipine besylate and olmesartan medoxomil) 5/20, 5/40, 10/20, and 10/40 mg Tablets.

We also refer to your submission dated December 8, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 27, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified potential review issues. We are providing the following comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. In accordance with CFR 314.50 (i)(1)(i)(A)(4), please submit a patent certification under Paragraph IV confirming that you own olmesartan medoxomil.
2. Provide a table cross-referencing the batch numbers to study numbers, batch size, and batch identification.
3. Submit a request for a biowaiver of bioequivalence studies for the intermediate strengths.
4. You state in your study report that the pharmacogenomics data collected for study 301 will not be submitted at this time. Please clarify why there will be a delay in submitting the data.
5. The established name, amlodipine besylate, and the strength (5 or 10 mg) do not match. The package insert and container labels should be revised and resubmitted accordingly.

b(4)

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 22-100

Page 2

If you have any questions, please call Ms. Denise Hinton, Regulatory Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

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

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Norman Stockbridge
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-100

Daiichi Sankyo Pharma Development
a division of Daiichi Sankyo Inc.
Attention: Mr. Tetsuya (Ted) Kaiso
Manager, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Mr. Kaiso:

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

Name of Drug Product: Azor (amlodipine besylate and olmesartan medoxomil) 5/20, 5/40, 10/20 and 10/40 mg Tablets

Review Priority Classification: Standard (S)

Date of Application: November 27, 2006

Date of Receipt: November 27, 2006

Our Reference Number: NDA 22-100

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 January 26, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 27, 2007.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

NDA 22-100

Page 2

Please cite the NDA number listed above 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

If you have any questions, please contact:

Ms. Denise Hinton
Regulatory Health Project Manager
(301) 796-1090

Sincerely,

{See appended electronic signature page}

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

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Edward Fromm

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IND 70,410
CS-8663
Daiichi Sankyo, Inc.

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IND 70, 410
CS-8663
Daiichi Sankyo Pharma Development
Type B Pre-NDA Meeting Minutes

Application Number: IND 70,410

Sponsor: Daiichi-Sankyo, Inc.

Drug: CS-8663 Tablets
(olmesartan medoxomil and amlodipine besylate)

Type of Meeting: Type B

Classification: Pre-NDA

Meeting Request Date: July 6, 2006

Confirmation Date: July 20, 2006

Meeting Date: September 13, 2006

Time: 1:00 – 3:00 PM

Meeting Chair: Norman Stockbridge, M.D., Ph.D.

Meeting recorder: Denise Hinton

List of Attendees:

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Medical Officer
Albert DeFelice, Ph.D.	Team Leader, Pharmacology
Elena Mishina	Clinical Pharmacology/ Biopharmaceutics
Denise Hinton	Project Management Staff

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Daiichi-Sankyo

Howard Hoffman
Rich Cuprys
Tetsuya Kaiso
Francis Plat

Reinilde Heyrman, M.D.
Michael Melino, Ph.D.
Antonia Wang, Ph.D.
James Lee, Ph.D.
Paresh Patel
Jane Li, M.D.

Vice President, Regulatory Affairs
Executive Director, Regulatory Affairs
Manager, Regulatory Affairs
M.D., Vice President,
Cardiovascular Clinical Development
Executive Director, Clinical Development
Director, Clinical Development
Senior Director, Biostatistics
Staff Biostatistician, Biostatistics
Associate Director, Data Management
Senior Director, Risk Management

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DISCUSSION

Following introductions, the Sponsor presented slides of the proposal for the preNDA submission (slides attached).

Question 1: Adequacy of Non-Clinical Program

During the December 20, 2004 Guidance Meeting, the Agency agreed to the Daiichi Sankyo proposal to conduct one non-clinical study, a "bridging" three month repeated dose toxicity study in rats to evaluate synergistic toxic effects of the combination drug product (olmesartan medoxomil plus amlodipine besylate) relative to the individual components. Daiichi Sankyo communicated with the Agency on September 20, 2005 regarding the design of this study and obtained agreement on dosing.

Daiichi Sankyo proposes to submit the results from this study and to cross-reference all non-clinical information from NDA 21-286 for Benicar[®] (olmesartan medoxomil) and NDA 19-787 for Norvasc[®] (amlodipine besylate). Does the Agency agree that this is sufficient for the NDA filing?

FDA Preliminary Response

Yes

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the preliminary response.

Question 2: Adequacy of Clinical / Clinical Pharmacology Program

During the December 20, 2004 Guidance Meeting, the Agency agreed that the proposed phase 3 factorial design study (CS8663-A-U301) and the clinical pharmacology program were sufficient, pending review, to support registration of the fixed combination product. Daiichi Sankyo believes that the outlined development program is sufficient to support the filing of this NDA for the treatment of hypertension - not for initial therapy. Does the Agency agree?

FDA Preliminary Response;

Yes.

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the Agency's preliminary response.

Question 3: Adequacy of Clinical Development Program for Additional Indication
Based on the observed safety and efficacy results obtained from study CS-8663 A-U301, and JNC-7 guidelines for the treatment of hypertension, Daiichi Sankyo believes that the study data is adequate, pending review, to support an additional indication for the initial therapy of hypertension in patients with Stage 2 hypertension (BP 160/100mmHg). Does the Agency agree?

Preliminary Response

No, however this is subject to change by a complete review. Our quick evaluation of your data is that, while they show very reasonable incremental reductions in blood pressure of the combination compared to the monotherapies, they do not show that blood pressure control is futile with the monotherapies and that control is reached much quicker.

Discussion during Face to Face Meeting

The Sponsor presented clinical efficacy data from the study CS8663-A-U301 in support of an additional indication for the initial therapy of hypertension in patients with Stage 2 hypertension (BP \geq 160/100 mmHg).

The Agency commented as follows:

- The Division is open to review data in the NDA in support of initial therapy for stage 2 hypertension (BP \geq 160/100 mmHg)
- Submission of the additional indication would not delay the review of the primary indication for the treatment of hypertension.
- If the additional indication is not approvable, it would not impact the approvability of the primary indication (including "not for initial therapy").
- At this time, the Agency does not require the Sponsor to conduct an additional study in support of the additional indication for initial therapy in stage 2 hypertensive patients.
- The Division is reviewing its position for fixed dose combination products specific to data requirements in support of an indication for initial therapy of hypertension, and looking across previously completed factorial design clinical trials to evaluate BP vs. AE rates.

Question 4: Adequacy of Patient Exposure for Safety Evaluation

During the December 20, 2004 Guidance Meeting, the Agency agreed to the adequacy of the safety program that was presented specific to patient exposure. Daiichi Sankyo believes that the extent and duration of patient exposure from the phase 3 study is sufficient for the NDA filing. Does the Agency agree?

Preliminary Response

Yes.

Discussion during Face to Face Meeting

The sponsor had no comments regarding our response.

Question 5: Adequacy of Special Safety Evaluation

Based on the therapeutic class of the drugs studied, Daiichi Sankyo has specifically evaluated AEs related to possible excessive therapeutic effects of the combination product. These include hypotension, dizziness, syncope, as well as renal and hepatic function and edema. Does the Agency request any additional special group assessments?

FDA Preliminary Response

No, the special group assessments proposed are reasonable.

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the Agency's preliminary response.

Question 6: Adequacy of Edema Evaluation

Daiichi Sankyo pre-specified the safety evaluation of edema in the pivotal study and included the use of a categorical scale for collecting and assessing the incidence of edema. This proactive methodological approach generated a considerably higher incidence of edema in all active and placebo groups. These results are not comparative to historical clinical study data obtained from passive AE observations, or to what is listed in the current product labeling for the individual components or for combination products that may contain one of these components. Accordingly, Daiichi Sankyo would like to highlight these observations to the Agency, in advance of the NDA review. We request Agency guidance on the need for any additional analyses and the appropriate presentation of this information in the product labeling.

FDA Preliminary Response

The analyses presented appear adequate. You should include a presentation of these data in the proposed labeling, but the final wording of the label will depend upon our evaluation of the data.

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Discussion during Face to Face Meeting

The Sponsor presented the pro-active method used to collect and assess the incidence of edema in the study CS8663-A-U301 and provided the following approach for the presentation of proposed product labeling in the NDA:

- The edema information will be included in a separate section and not be repeated in the AE table.
- Proposed labeling subsection for edema will include an explanation of the pro-active collection and assessment of edema and rationale.
- Proposed labeling will include a table or graphical representation of the placebo-subtracted incidence of edema for the respective monotherapies, and for the fixed drug combinations intended for US commercialization.
- The Sponsor proposed to provide labeling text related to the observed reduction of edema incidence with CS-8663 compared to monotherapy with AML 10 mg using placebo-subtracted incidence rates. The Division indicated that it would accept this information for review.

Overall, the Division confirmed that this matter is a review issue, but the approach presented seems acceptable. Additionally, we commented that actual wording for the observed reduction of edema incidence with CS-8663 will be a review issue.

Question 7: Risk Management Plan

Based on the safety results obtained from completed non-clinical and clinical studies in this development program, as well as the well characterized safety profile of each individual active drug component (olmesartan medoxomil and amlodipine besylate), Daiichi Sankyo believes that a standard pharmacovigilance approach suffices for monitoring adverse drug reactions for the marketed product. Daiichi Sankyo believes that a risk management plan is not required for the NDA. Does the Agency agree?

FDA Preliminary Response

Yes.

Discussion during Face to Face Meeting

No further discussion. The Sponsor agreed with the preliminary comments.

Question 8: Adequacy of Chemistry, Manufacturing and Controls

Question 8.1: Drug product specifications

Daiichi Sankyo will provide the proposed release and stability specifications for the drug product. Does the Agency agree that these specifications are acceptable to support the NDA filing?

FDA Preliminary Response

The final assessment of drug product specification will be made during the NDA review. However, please note the following:

Regarding dissolution, the final specification (rpm and Q value) will be determined based on the relevant batch data as well as dissolution testing at 50 rpm and 75 rpm speeds obtained from stability studies. Please note that FDA recommends collecting dissolution data for each strength and time point from 12 individual tablets.

The proposed content uniformity format and specifications are not clear. At this time we do not have access to the requirements of USP 30. If the proposed content uniformity specification comply with the forthcoming USP 30 to be effective from January 2007, then it should be acceptable.

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the preliminary response.

Question 8.2: Extension of Expiry Dates

Daiichi Sankyo proposes the extension of expiry dates based on pilot registration batches and statistical analysis of accumulated real time data. Does the Agency agree with this approach?

FDA Preliminary Response

The Agency agrees with the proposed approach for assignment of expiry date during NDA review. However, according to the section XI. A. 4 of Guidance for Industry Changes to an Approved NDA or ANDA, an extension of expiry date on pilot scale batches is submitted via Prior Approval Supplement.

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the preliminary response.

Question 9: General Topics

Question 9.1: Adequacy of 505(b)(2) Submission

As agreed by the Agency during the December 20, 2004 Guidance Meeting, the proposed NDA will be submitted pursuant to section 505(b)(2). In addition, to the results from the completed clinical program, Daiichi Sankyo proposes to cross-reference all clinical information from NDA 21-286 for Benicar[®] and NDA 19-787 for Norvasc[®]. Does the Agency agree that this is sufficient for the NDA filing?

FDA Preliminary Response

Yes.

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the preliminary response.

Question 9.2: Confirmation of Pediatric Waiver

During the meeting of December 20, 2004, the Agency agreed to waive the need for evaluation of CS-8663 in the pediatric population. Does the Agency confirm this position?

FDA Preliminary Response

Yes.

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the preliminary response.

Question 9.3: Labeling Format

In accordance with the January 2006 *Final Rule on the Requirements for Prescribing Information for Prescribing Information for Drug and Biological Products*, Daiichi Sankyo is providing draft labeling in this new format for the Agency's feedback (see Appendix 13). Does the Agency agree to review this draft labeling and provide guidance?

FDA Preliminary Response

The labeling resulting from this submission must be consistent with the January 2006 Final Rule. We note that the draft labeling you included in this submission does not include a highlights section. Please ensure that the labeling submitted with the NDA is completely consistent with the January 2006 Final Rule.

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the preliminary response.

Question 9.4: Use of SNOMED

We request Agency guidance on the requirement for the use of Systematized Nomenclature of Medicine (SNOMED) to code terms in the product labeling. Daiichi Sankyo proposes to submit the results from this study and to cross-reference all non-clinical information from NDA 21-286 for Benicar® (olmesartan medoxomil) and NDA 19-787 for Norvasc® (amlodipine besylate). Does the Agency agree that this is sufficient for the NDA filing?

FDA Preliminary Response

The Agency does not require you to use SNOMED; however you may refer to the following link, <http://www.fda.gov/oc/datacouncil/cdsys.html>, for the code terms. The code system OID is 2.16.840.1.113883.6.96.

This SPL terminology page informs browsers about the problem list subset of SNOMED:
<http://www.fda.gov/oc/datacouncil/term.html#med>

Refer to <http://www.fda.gov/oc/datacouncil/spl.html> for the list of contact information to receive assistance with PLR SPL.

Additional advice and assistance with SPL should be directed to the following email address: spl@fda.hhs.gov

Discussion during Face to Face Meeting

The Division reiterated that the use of MedDRA will be acceptable for the Highlight section of the proposed labeling.

Question 9.5: Presentation of the Data

The NDA provides clinical and CMC information for six different strengths of the drug product, listed below; however Daiichi Sankyo does not intend to market the two lower combination doses containing 10 mg of olmesartan medoxomil*.

Olmesartan medoxomil 40 mg + Amlodipine besylate 5 mg
Olmesartan medoxomil 40 mg + Amlodipine besylate 10 mg
Olmesartan medoxomil 20 mg + Amlodipine besylate 5 mg
Olmesartan medoxomil 20 mg + Amlodipine besylate 10 mg
*Olmesartan medoxomil 10 mg + Amlodipine besylate 5 mg
*Olmesartan medoxomil 10 mg + Amlodipine besylate 10 mg

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Daiichi Sankyo proposes to present information specific to the combination doses intended for US commercial distribution only in the product labeling and Environmental Analysis Report. Does the Agency agree with this approach?

FDA Preliminary Response

Yes.

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the preliminary response.

Question 9.6: TOC of ISE and ISS

A proposed draft table of contents (TOC) for the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) will be provided in the meeting information package as Appendix 14. Daiichi Sankyo requests Agency feedback on the adequacy of the TOC.

FDA Preliminary Response

The TOC appears to be reasonable, although we note that there is not a specific subheading in the ISE for characterizing the effects of the combination throughout the interdosing interval, e. g., peak/trough effects, ABPM, etc.

Discussion during Face to Face Meeting

Regarding characterizing the effects of the combination throughout the interdosing interval in the ISE, the Sponsor explained that it measured the blood pressure at peak at

week 8 in the PK/PD substudy of CS8663-A-U301 for approximately 500 patients. The preliminary results of trough-to-peak ratio for Δ BP (DBP/SBP) from PK substudy was presented (all trough-to-peak ratios were approximately 0.8). FDA confirmed that the trough-to-peak ratio data are acceptable for review.

Question 9.7: Patient Package Insert

For certain drug products, a Patient Package Insert that contains information to aid a patient's understanding on how to safely use a drug is required. Daiichi Sankyo requests Agency guidance on the requirement for a Patient Package Insert for this combination product.

FDA Preliminary Response

A PPI is not required.

Discussion during Face to Face Meeting

There was no further discussion. The Sponsor agreed with the FDA preliminary response.

Question 9.8: SAS Version

We request Agency agreement that study raw data and derived variables can be submitted in Version 5 SAS transport format according to FDA guidance, and the data structure prepared is sponsor-defined and not SDTM 3.0.

FDA Preliminary Response

The SAS transport files do not need to be SDTM 3.0 format. However, please provide Acrobat PDF files with variable and code definitions, an annotated CRF showing the variables included, and the analysis files and SAS programs for all efficacy analysis.

Discussion during Face to Face Meeting

The Sponsor agreed that an annotated CRF, including variables, along with the analysis files and SAS programs for all efficacy analyses will be submitted.

The Division agreed with the Sponsor's proposal to include variable and decode definitions within DEFINE.PDF, and to provide SAS format catalogue and FORMAT.SAS code to facilitate data decoding.

Question 9.9: eCTD format

Daiichi Sankyo intends to submit CS-8663 in eCTD format. Daiichi Sankyo requests a waiver of the requirement to provide an eCTD sample submission.

who will be compiling this eCTD, has filed an acceptable eCTD pilot with the Agency on October 29, 2004 (pilot no. 90031). Does the Agency agree with our request for a waiver?

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FDA Preliminary Response

Yes, although we would still recommend a sample submission. Additionally, please ensure that case report form (CRF) submissions for deaths and withdrawals are complete and include all information submitted to you regarding adverse events regardless of whether the information was arbitrarily labeled a "case report form". For example, serious adverse event forms labeled "SAE worksheets" are CRFs. Medwatch-type forms used for expedited reporting during the trial are also CRFs and should be submitted. All CRFs for a patient should be stored in one location in the NDA submission and should be easily accessible by the patient's study ID.

Discussion during Face to Face Meeting

The Division indicated that it was the best interest of the Sponsor to submit a sample eCTD. The Sponsor will provide a sample submission of the eCTD for review before the NDA submission. The Division clarified that the purpose of the sample submission was to ensure that the eCTD XML backbones are acceptable.

The Sponsor agreed to submit all information on deaths and withdrawals due to any AE, including CRFs, MedWatch-type forms and SAE worksheets (SAVER).

Meeting Chair: {See appended electronic signature page}
Denise M. Hinton

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

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TAM 10/12/06
EU 10/12/06
NS 10/13/06

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CS-8663

Pre-NDA meeting

Sponsor Updates to FDA Responses

1. Adequacy of Non-Clinical Program – Agreed
2. Adequacy of Clinical / Clinical Pharmacology Program – Agreed
3. Adequacy of Clinical Development Program for Additional Indication – To be discussed
4. Adequacy of Patient Exposure for Safety Evaluation – Agreed
5. Adequacy of Special Safety Evaluation – Agreed
6. Adequacy of Edema Evaluation – To be discussed
7. Risk Management Plan – Agreed
8. Adequacy of Chemistry, Manufacturing and Controls – Agreed

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Sponsor Updates to FDA Responses

9. General Topics
- 9.1. Adequacy of 505(b)(2) Submission – Agreed
- 9.2. Confirmation of Pediatric Waiver – Agreed
- 9.3. Labeling Format – Agreed
- 9.4. Use of SNOMED – To be discussed
- 9.5. Presentation of the Data – Agreed
- 9.6. TOC of ISE and ISS – To be discussed
- 9.7. Patient Package Insert – Agreed
- 9.8. SAS Version – To be discussed
- 9.9. eCTD format – To be discussed

9.4. Use of SNOMED

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9.4. Use of SNOMED

- Daiichi Sankyo Question
 - We request Agency guidance on the requirement for the use of Systematized Nomenclature of Medicine (SNOMED) to code terms in the product labeling.
- FDA Preliminary Response
 - The Agency does not require you to use SNOMED; however you may refer to the following link,

SNOMED

- We would like to confirm that we are NOT required to use SNOMED for the highlight section of labeling – MedDRA will be acceptable.

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9.8. SAS Version

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9.8. SAS Version

- Daiichi Sankyo Question
 - We request Agency agreement that study raw data and derived variables can be submitted in Version 5 SAS transport format according to FDA guidance, and the data structure prepared is sponsor-defined and not SDTM 3.0.
- FDA Preliminary Response
 - The SAS transport files do not need to be SDTM 3.0 format. However, please provide Acrobat PDF files with variable and code definitions, an annotated CRF showing the variables included, and the analysis files and SAS programs for all efficacy analysis.

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Proposals

- Annotated CRF showing the variables included, and the analysis files and SAS programs for all efficacy analyses will be submitted.
- We propose to include variable and decode definitions within DEFINE.PDF.
- We propose to provide SAS format catalogue and FORMAT.SAS code to aid easy data decoding.

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9.9. eCTD format

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9.9. eCTD format

- Daiichi Sankyo Question
 - Daiichi Sankyo intends to submit CS-8663 in eCTD format. Daiichi Sankyo requests a waiver of the requirement to provide an eCTD sample submission. [redacted], who will be compiling this eCTD, has filed an acceptable eCTD pilot with the Agency on October 29, 2004 (pilot no. 90031). Does the Agency agree with our request for a waiver?
- FDA Preliminary Response
 - Yes, although we would still recommend a sample submission. Additionally, please ensure that case report form (CRF) submissions for deaths and withdrawals are complete and include all information submitted to you regarding adverse events regardless of whether the information was arbitrarily labeled a "case report form". For example, serious adverse event forms labeled "SAE worksheets" are CRFs. Medwatch-type forms used for expedited reporting during the trial are also CRFs and should be submitted. All CRFs for a patient should be stored in one location in the NDA submission and should be easily accessible by the patient's study ID.

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- Sample Submission
 - The proposed filing date is mid/end of November 2006.
 - We agree to provide the sample submission within 2 weeks, and request FDA feedback in a timely manner to accommodate our proposed filing date.
- CRF Submission
 - We would like to confirm that we will submit all the information on the deaths and withdrawals due to SAE, including CRFs, MedWatch-type forms and SAE worksheets (SAVER).

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9.6. TOC of ISE and ISS

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9.6. TOC of ISE and ISS

- Daiichi Sankyo Question
 - A proposed draft table of contents (TOC) for the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) will be provided in the meeting information package as Appendix 14. Daiichi Sankyo requests Agency feedback on the adequacy of the TOC.
- FDA Preliminary Response
 - The TOC appears to be reasonable, although we note that there is not a specific subheading in the ISE for characterizing the effects of the combination throughout the interdosing interval, e.g., peak/trough effects, ABPM, etc.

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Calculation methodology for trough-to-peak ratio

- We measured the blood pressure at peak at week 8 in the PK/PD substudy of CS8663-A-U301.
- This substudy included approximately 500 patients.
- Blood pressure measurements and plasma concentration were obtained at peak for olmesartan (0.5-2 hours post dose) and for amlodipine (4-10 hours post dose).
- In general, maximum BP lowering effect occurred during 4-10 hours post dose.
- Trough/peak = Week 8 trough change from baseline / Week 8 at 4-10 hr change from baseline

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Trough-to-peak ratio for BP (DBP/SBP) from PK substudy

	PBO OM (N)	10 mg OM (N)	20 mg OM (N)	40 mg OM (N)
PBO AML (N)	-- / -- (32)	0.84/ 1.01 (41)	0.75/ 0.81 (42)	0.63/ 0.76 (42)
5 mg AML (N)	0.78/ 0.80 (40)	0.80/ 0.86 (59)	0.74/ 0.81 (46)	0.77/ 0.92 (47)
10 mg AML (N)	0.88/ 1.07 (43)	0.77/ 0.79 (46)	0.81/ 0.85 (43)	0.78/ 0.86 (50)

Trough/peak = Week 8 trough change from baseline / Week 8 at 4-10 hr change from baseline

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6. Adequacy of Edema Evaluation

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6. Adequacy of Edema Evaluation

- Daiichi Sankyo Question
 - Daiichi Sankyo pre-specified the safety evaluation of edema in the pivotal study and included the use of a categorical scale for collecting and assessing the incidence of edema. This proactive methodological approach generated a considerably higher incidence of edema in all active and placebo groups. These results are not comparative to historical clinical study data obtained from passive AE observations, or to what is listed in the current product labeling for the individual components or for combination products that may contain one of these components. Accordingly, Daiichi Sankyo would like to highlight these observations to the Agency, in advance of the NDA review. We request Agency guidance on the need for any additional analyses and the appropriate presentation of this information in the product labeling.
- FDA Preliminary Response
 - The analysis presented appear adequate. You should include a presentation of these data in the proposed labeling, but the final wording of the label will depend upon our evaluation of the data.

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Edema: CRF collection at each visit

- Does the subject have peripheral edema present?
 1 Yes* 0 No
 - *If edema was not present at screening, or if there is a clinically significant change from screening, record on the Adverse Events CRF.
- If yes, grade on the following scale:
 - 1 Mild pitting, slight indentation
 - 2 Moderate pitting, slight indentation
 - 3 Deep pitting, indentation remains swollen
 - 4 Deep pitting, leg very swollen

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Comparison of the results from the pivotal study to available data

Study	Studies with pro-active evaluation of edema		Data obtained via passive collection of AE during studies										
	CS-8663	VALIUS [®]	Nivolumab			Ipilimumab			Lenvatinib		Lapatinib		
	VALUE VALIUS 10 mg (n=144)	VALUE VALIUS 10 mg (n=144)	Normal to normal (n=72)	Normal to mild (n=72)	Normal to moderate (n=72)	Normal to mild (n=72)	Normal to moderate (n=72)						
Edema	12.3	14.9	22.9	15.0	10.8	9.6	+1.8	2.1	3.1	2.2			
Dizziness	2.3	3.6	16.3	19.3	3.4	1.4	1.3	3.9	1.3	2.3	1.3		
Headache	4.3	14.2	14.3	12.3			1.3	7.8	+1.8	2.2	2.9	3.6	

* Fisher S, Gijbels S, Wilber JL, et al. Outcomes in hepatocellular carcinoma in high performance risk treated with regorafenib vs sorafenib or sunitinib: the VALUE randomized trial. *Lancet* 2016; 387: 2022-2031.
 All AEs were considered pre-specified AEs during the VALUE trial.

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Edema: Proposed Product Labeling (1/2)

- Edema should be analyzed differently and presented separately from other AEs due to:
 - Pro-active and aggressive method of collecting and evaluating edema
 - Observed incidences of edema in all treatment groups, including the placebo group (12.3%), are higher than and inconsistent with historical clinical data (Product labeling, other studies)
 - Placebo-subtraction will allow for better comparison with historical data, to facilitate understanding and avoid confusion by practitioners
 - Placebo-subtraction renders the reduction in edema associated with combining an ACE-I/ARB to amlodipine 10 mg comparable to historical data, to facilitate understanding by practitioners

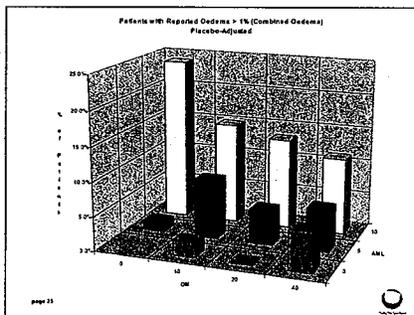
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Edema: Proposed Product Labeling (2/2)

- Labeling subsection for edema will include an explanation of pro-active collection of edema and rationale
- Labeling will include a table or graphical representation of placebo-subtracted incidence of AE of edema for respective monotherapies, 20/5, 40/5, 20/10, and 40/10
- Labeling will include text on observed reduction of edema incidence with CS-8663 compared to monotherapy with AML 10 mg using placebo-subtracted incidence rates
- We propose the edema information be included in a separate section and not be repeated in the AE table

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3. Adequacy of Clinical Development Program for Additional Indication

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3. Adequacy of Clinical Development Program for Additional Indication

- Daiichi Sankyo Question
 - Based on the observed safety and efficacy results obtained from study CS8663-A-U301, and JNC-7 guidelines for the treatment of hypertension, Daiichi Sankyo believes that the study data is adequate, pending review, to support an additional indication for the initial therapy of hypertension in patients with Stage 2 hypertension (BP $\geq 160/100$ mmHg). Does the Agency agree?
- FDA Preliminary Response
 - No, however this is subject to change by a complete review. Our quick evaluation of your data is that, while they show very reasonable incremental reductions in blood pressure of the combination compared to the monotherapies, they do not show that blood pressure control is faster with monotherapies and that control is reached much quicker.

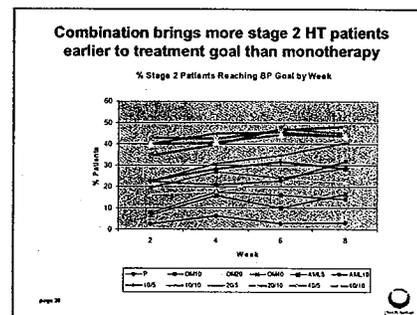
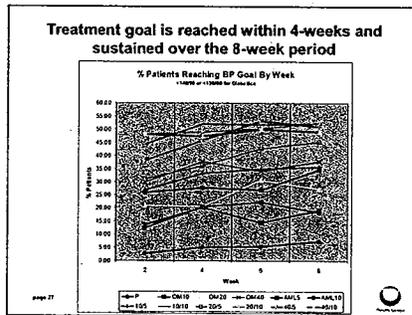
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Adequacy of Development Program for Additional Indication (stage 2 hypertension)

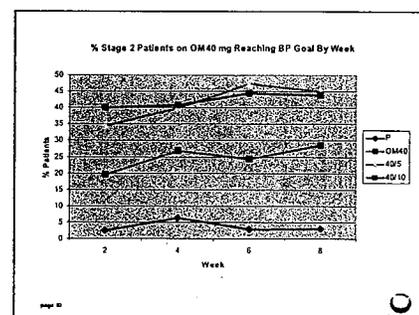
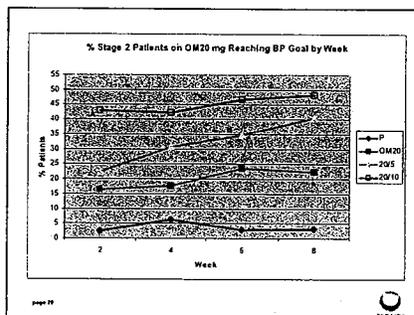
- JNC7: Treatment algorithm
 - Lifestyle modifications
 - When BP is > 20 mmHg above systolic goal or 10 mmHg above diastolic goal (stage 2 HT), consideration should be given to initiate therapy with two drugs, either as separate prescriptions or in fixed-dose combinations
- Why start with a combination of ARB and CCB?
 - Treating BP to target $< 140/90$ mmHg is associated with a decrease in CVD complications
 - More than 2/3 of HT patients will require 2 or more antihypertensive agents to control BP
 - The initiation of therapy with more than one drug increases the likelihood of achieving BP goal in a more timely fashion

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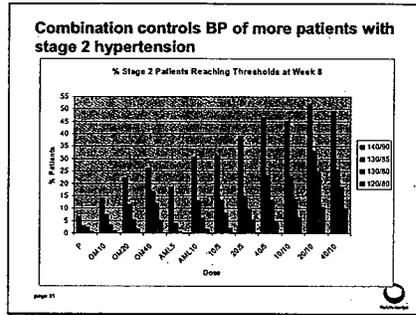
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Stage 2 HT patients reach goal 50% more frequently on CS-8663 than on monotherapy

	PBO OM (N)	10 mg OM (N)	20 mg OM (N)	40 mg OM (N)
PBO AML (N)	5.3% (133)	13.1% (122)	21.4% (131)	25.4% (118)
5 mg AML (N)	15.3% (124)	27.4% (135)	36.7% (128)	44.2% (120)
10 mg AML (N)	29.2% (130)	40.9% (126)	49.2% (132)	43.8% (128)

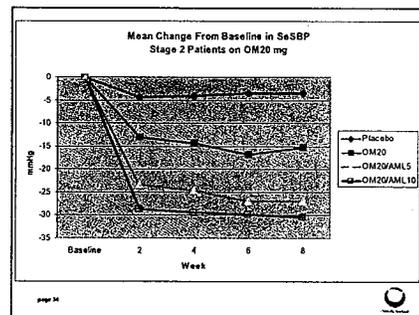
After 8 weeks of treatment

Slide 17

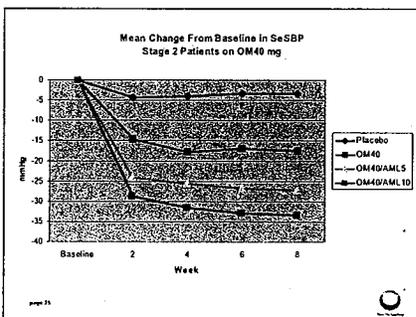
Stage 2 HT patients reach threshold of 130/80 more frequently on CS-8663 than on monotherapy

	PBO OM (N)	10 mg OM (N)	20 mg OM (N)	40 mg OM (N)
PBO AML (N)	2.3% (133)	3.3% (122)	5.3% (131)	11.7% (118)
5 mg AML (N)	0.8% (124)	8.2% (135)	9.4% (128)	13.3% (120)
10 mg AML (N)	6.2% (130)	13.5% (126)	24.2% (132)	18.8% (128)

After 8 weeks of treatment



Slide 18



Safety: AE in stage 2 hypertensive patients

	PBO OM	10 mg OM	20 mg OM	40 mg OM
PBO AML	79 (59.4%)	84 (52.0%)	74 (55.6%)	59 (49.2%)
5 mg AML	59 (47.2%)	60 (44.4%)	72 (56.3%)	63 (51.2%)
10 mg AML	76 (58.5%)	74 (58.7%)	73 (54.5%)	72 (55.8%)

During 8 weeks of treatment

Slide 19

SAE in stage 2 hypertensive patients

	PBO OM (N)	10 mg OM (N)	20 mg OM (N)	40 mg OM (N)
PBO AML (N)	2	1	3	1
5 mg AML (N)	0	0	1	2
10 mg AML (N)	1	3	3	5

During 8 weeks of treatment

**Discontinuations due to AEs
 in stage 2 hypertensive patients**

Group	N	%
Placebo	21	15.8%
Monotherapy	50	7.9%
Combination	22	2.8%

During 8 weeks of treatment

Slide 20

**Hypotension/orthostatic hypotension
 in stage 2 hypertensive patients**

	PBO OM (N)	10 mg OM (N)	20 mg OM (N)	40 mg OM (N)
PBO AML (N)	0	0	0	0
5 mg AML (N)	0	0	0	0
10 mg AML (N)	1	1	2	2

During 8 weeks of treatment

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/s/

Denise Hinton

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Norman Stockbridge

10/13/2006 08:38:39 PM

IND 70, 410
CS-8663
Daiichi Sankyo Pharma Development
Type B Pre-NDA Meeting
Preliminary Responses

"This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 13, 2006 from 1:00-3:00 PM between Daiichi Sankyo Pharma, Inc. and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to 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 the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principle questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan, the purpose of the meeting, and/or to the questions] (based on our responses herein), we may not be able to reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. 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 to discuss the possibility of including these for discussion at the meeting."

DISCUSSION

1. Adequacy of Non-Clinical Program

Daiichi Sankyo proposes to submit the results from this study and to cross-reference all non-clinical information from NDA 21-286 from Benicar (olmesartan medoxomil) and NDA 19-787 for Norvasc (amlodipine besylate). Does the Agency agree that this is sufficient for the NDA filing?

Preliminary Response

Yes.

2. Adequacy of Clinical/Clinical Pharmacology Program

During the December 20, 2004 Guidance Meeting, the Agency agreed that the proposed phase 3 factorial design study (CS8663-A-U301) and the clinical pharmacology program were sufficient, pending review, to support registration of the fixed combination product. Daiichi Sankyo believes that the outlined development program is sufficient to support the filing of this NDA for the treatment of hypertension- not for initial therapy. Does the Agency agree?

Preliminary Response

Yes.

3. Adequacy of Clinical Development Program for Additional Indication

Based on the observed safety and efficacy results obtained from study CS-8663 A-U301, and JNC-7 guidelines for the treatment of hypertension, Daiichi Sankyo believes that the study data is adequate, pending review, to support an additional indication for the initial therapy of hypertension in patients with Stage 2 hypertension (BP 160/100mmHg). Does the Agency agree?

Preliminary Response

No, however this is subject to change by a complete review. Our quick evaluation of your data is that, while they show very reasonable incremental reductions in blood pressure of the combination compared to the monotherapies, they do not show that blood pressure control is futile with the monotherapies and that control is reached much quicker.

4. Adequacy of Patient Exposure for Safety Evaluation

During the December 20, 2004 Guidance Meeting, the Agency agreed to the adequacy of the safety program that was presented specific to patient exposure. Daiichi Sankyo believes that the extent and duration of patient exposure from the phase 3 study is sufficient for the NDA filing. Does the Agency agree?

Preliminary Response

Yes.

5. Adequacy of Patient Exposure for Safety Evaluation

Based on the therapeutic class of the drugs studied, Daiichi Sankyo has specifically evaluated AEs related to possible excessive therapeutic effects of the combination product. These include hypotension, dizziness, syncope, as well as renal and hepatic function and edema. Does the Agency request any additional special group assessments?

Preliminary Response

No, the special group assessments proposed are reasonable.

6. Adequacy of Edema Evaluation

Daiichi Sankyo pre-specified the safety evaluation of edema in the pivotal study and included the use of a categorical scale for collecting and assessing the incidence of edema. This proactive methodological approach generated a

considerably higher incidence of edema in all active and placebo groups. These results are not comparative to historical clinical study data obtained from passive AE observations, or to what is listed in the current product labeling for the individual components or for combination products that may contain one of these components. Accordingly, Daiichi Sankyo would like to highlight these observations to the Agency, in advance of the NDA review. We request Agency guidance on the need for any additional analyses and the appropriate presentation of this information in the product labeling.

Preliminary Response

The analyses presented appear adequate. You should include a presentation of these data in the proposed labeling, but the final wording of the label will depend upon our evaluation of the data.

7. Risk Management Plan

Based on the safety results obtained from completed non-clinical and clinical studies in this development program, as well as the well characterized safety profile of each individual active drug component (olmesartan medoxomil and amlodipine besylate), Daiichi Sankyo believes that a standard pharmacovigilance approach suffices for monitoring adverse drug reactions for the marketed product. Daiichi Sankyo believes that a risk management plan is not required for the NDA. Does the Agency agree?

Preliminary Response

Yes.

8. Adequacy of Chemistry, Manufacturing and Controls

8.1 Drug product specifications

Daiichi Sankyo will provide the proposed release and stability specifications for the drug product. Does the Agency agree that these specifications are acceptable to support the NDA filing?

Preliminary Response

The final assessment of drug product specification will be made during the NDA review. However, please note the following:

Regarding dissolution, the final specification (rpm and Q value) will be determined based on the relevant batch data as well as dissolution testing at 50 rpm and 75 rpm speeds obtained from stability studies. Please note that FDA recommends collecting dissolution data for each strength and time point from 12 individual tablets.

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The proposed content uniformity format and specifications are not clear. At this time we do not have access to the requirements of USP 30. If the proposed content uniformity specification comply with the forthcoming USP 30 to be effective from January 2007, then it should be acceptable.

8.2 Extension of Expiry Dates

Daiichi Sankyo proposes the extension of expiry dates based on pilot registration batches and statistical analysis of accumulated real time data. Does the Agency agree with this approach?

Preliminary Response

FDA agrees with the proposed approach for assignment of expiry date during NDA review. However, according to the section XI.A.4 of Guidance for Industry Changes to an Approved NDA or ANDA, an extension of expiry date on pilot scale batches is submitted via Prior Approval Supplement.

9. General Topics

Adequacy of 505(b)(2) Submission

As agreed by the Agency during the December 20, 2004 Guidance Meeting, the proposed NDA will be submitted pursuant to section 505(b)(2). In addition, to the results from the completed clinical program, Daiichi Sankyo proposes to cross-reference all clinical information from NDA 21-286 for Benicar and NDA 19-787 for Norvasc. Does the Agency agree that this is sufficient for the NDA filing?

Preliminary Response

Yes.

9.2 Confirmation of Pediatric Waiver

During the meeting of December 20, 2004, the Agency agreed to waive the need for evaluation of CS-8663 in the pediatric population. Does the Agency confirm this position?

Preliminary Response

Yes.

9.3 Labeling format

In accordance with the January 2006 *Final Rule on the Requirements for Prescribing Information for Drug and Biological Products*, Daiichi Sankyo is providing draft labeling in this new format for the Agency's feedback (see Appendix 13). Does the Agency agree to review this draft labeling and provide guidance?

Preliminary Response

The labeling resulting from this submission must be consistent with the January 2006 Final Rule. We note that the draft labeling you included in this submission does not include a highlights section. Please ensure that the labeling submitted with the NDA is completely consistent with the January 2006 Final Rule.

9.4 Use of SNOMED

We request Agency guidance on the requirement for the use of Systematized Nomenclature of Medicine (SNOMED) to code terms in the product labeling.

Preliminary Response

The Agency does not require you to use SNOMED; however you may refer to the following link, <http://www.fda.gov/oc/datacouncil/cdsys.html>, for the code terms. The code system OID is 2.16.840.1.113883.6.96.

The following is a list of SPL resource information:

This SPL terminology page informs browsers about the problem list subset of SNOMED:
<http://www.fda.gov/oc/datacouncil/term.html#med>

Refer to <http://www.fda.gov/oc/datacouncil/spl.html> for the list of contact information to receive assistance with PLR SPL.

Additional advice and assistance with SPL should be directed to the following email address: spl@fda.hhs.gov

9.5 Presentation of the Data

The NDA provides clinical and CMC information for six different strengths of the drug product, listed below; however Daiichi Sankyo does not intend to market the two lower combination doses containing 10 mg of olmesartan medoxomil*.

Olmesartan medoxomil 40 mg + Amlodipine besylate 5 mg
Olmesartan medoxomil 40 mg + Amlodipine besylate 10 mg
Olmesartan medoxomil 20 mg + Amlodipine besylate 5 mg
Olmesartan medoxomil 20 mg + Amlodipine besylate 10 mg
***Olmesartan medoxomil 10 mg + Amlodipine besylate 5 mg**
***Olmesartan medoxomil 10 mg + Amlodipine besylate 10 mg**

b(4)

Daiichi Sankyo proposes to present information specific to the combination doses intended for US commercial distribution only in the product labeling and Environmental Analysis Report. Does the Agency agree with this approach?

Preliminary Response

Yes.

9.6 TOC of ISE and ISS

A proposed draft table of contents (TOC) for the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) will be provided in the meeting information package as Appendix 14. Daiichi Sankyo requests Agency feedback on the adequacy of the TOC.

Preliminary Response

The TOC appears to be reasonable, although we note that there is not a specific subheading in the ISE for characterizing the effects of the combination throughout the interdosing interval, e.g., peak/trough effects, ABPM, etc.

9.7 Patient Package Insert (PPI)

For certain drug products, a PPI that contains information to aid a patient's understanding on how to safely use a drug is required. Daiichi Sankyo requests Agency guidance on the requirement for a PPI for this combination product.

Preliminary Response

A PPI is not required.

9.8 SAS Version

We request Agency agreement that study raw data and derived variables can be submitted in Version 5 SAS transport format according to FDA guidance, and the data structure prepared is sponsor-defined and not SDTM 3.0.

Preliminary Response

The SAS transport files do not need to be SDTM 3.0 format. However, please provide Acrobat PDF files with variable and code definitions, an annotated CRF showing the variables included, and the analysis files and SAS programs for all efficacy analyses.

9.9 eCTD format

Daiichi Sankyo intends to submit CS-8663 in eCTD format. Daiichi Sankyo requests a waiver of the requirements to provide an eCTD sample submission. who will be compiling this eCTD, has filed an acceptable eCTD pilot with the Agency on October 29, 2004 (pilot no. 90031). Does the Agency agree with our request for a waiver?

b(4)

Preliminary Response

Yes, although we would still recommend a sample submission. Additionally, please ensure that case report form (CRF) submissions for deaths and withdrawals are complete and include all information submitted to you regarding adverse events regardless of whether the information was arbitrarily labeled a "case report form". For example,

IND 70,410
CS-8663
Daiichi Sankyo, Inc.

- 8 -

serious adverse event forms labeled "SAE worksheets" are CRFs. Medwatch-type forms used for expedited reporting during the trial are also CRFs and should be submitted. All CRFs for a patient should be stored in one location in the NDA submission and should be easily accessible by the patient's study ID.

If you have any questions, please call:

Denise M. Hinton
Regulatory Health Project Manager
(301) 796-1090

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,410

Daiichi-Sankyo Pharma Development
Attention: Paulette F. Kosmoski
Senior Director, Regulatory Affairs - CMC
399 Thornall Street
Edison, NJ 08837

Dear Ms. Kosmoski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CS-8663 Tablets, (olmesartan medoxomil and amlodipine besylate).

We also refer to the meeting between representatives of your firm and the FDA on July 27, 2006. The purpose of the meeting was to discuss the Chemistry, Manufacturing and Controls development strategy needed to support registration of your CS-8663 tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{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
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 27, 2006
TIME: 1:30 pm - 2:30 pm
LOCATION: Food and Drug Administration, White Oak Campus
APPLICATION: IND 70,410
SPONSOR: Daiichi-Sankyo Pharma Development
DRUG NAME: CS-8663 Tablets
TYPE OF MEETING: CMC specific End of Phase 2 Type B
MEETING CHAIR: Ramesh Sood, Ph.D.
Branch Chief, DPMA I
MEETING RECORDER: Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality, DPMA I

FDA ATTENDEES:

CENTER FOR DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Division of Pre-Marketing Assessment I

Ramesh Sood, Ph.D., Branch Chief

Kasturi Srinivasachar, Ph.D., Pharmaceutical Assessment Lead

Ramsharan D. Mittal, Ph.D., Review Chemist

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

Division of Pre-Marketing Assessment III & Manufacturing Science

Terrance Ocheltree, Ph.D. R.Ph., Review Chemist

DAIICHI-SANKYO PHARMA DEVELOPMENT ATTENDEES:

Wolfgang Bauer, Ph.D., Vice Director, Galenical Development

Takeshi Hamaura, Ph.D., Senior Director, Process Development/Product Formulation

Howard D. Hoffman, M.D., Vice President, US/EU & Regional Regulatory Affairs

Johann Lichey, Ph.D., Director, Galenical Development

Tetsuya Kaiso, Manager, Regulatory Affairs

Paulette Kosmoski, Senior Director, Regulatory Affairs-CMC

Andreas Teubner, Ph.D., Vice President, Pharmaceutical Development

Elmar Wadenstorfer, Ph.D., Director, Analytical Department

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BACKGROUND:

Daiichi-Sankyo Pharma Development, (Daiichi-Sankyo) is developing CS-8663 (olmesartan medoxomil and amlodipine besylate) tablets, proposed for the treatment of essential hypertension. Daiichi-Sankyo requested a Chemistry, Manufacturing and Controls (CMC) specific End of Phase 2 (type B) meeting on May 16, 2006, received May 17, 2006, to discuss Chemistry, Manufacturing and Controls development strategy needed to support registration. Daiichi-Sankyo submitted a pre-meeting CMC briefing document dated June 22, 2006, received June 23, 2006, providing additional information on discussion topics and questions. FDA provided written responses to all questions outlined in the briefing document on July 21, 2006, via email from Scott N. Goldie, Ph.D., (ONDQA) to Paulette F. Kosmoski, (Daiichi-Sankyo). These preliminary draft responses were archived in the administrative file. Daiichi-Sankyo and FDA discussed the responses at the face to face meeting on July 27, 2006.

MEETING DISCUSSION:

The questions from the Daiichi-Sankyo meeting package are related verbatim, with any additions in *italics* for clarity. The pre-meeting responses submitted by FDA to Daiichi-Sankyo are included for reference. Where additional discussion or clarification occurred during the meeting, a summary is recorded below. Slides used as discussion guides and presented during the meeting by Daiichi-Sankyo are included in the Appendix.

- | |
|---|
| <p>1. Is this approach (<i>as described in the meeting package</i>) to employ the Ph. Eur. Monograph standard and general chapter <5.4> for drug substance controls acceptable to the Agency for the alternate sourcing of the API?</p> |
|---|

FDA Preliminary Response: We do not agree with your proposal as specified in the meeting package since Ph. Eur. is not considered an official compendium by FDA. Justification for acceptance criteria should be provided based on actual data, scientific rationale, and FDA and ICH guidelines. Specifically we recommend that you:

1. Set residual solvent limits on the basis of actual data and not on maximum limits specified in ICH guidelines.
2. Demonstrate equivalency of particle size distribution characteristics between supplied drug substance. Also, demonstrate the equivalency of drug product regardless of drug substance supplier based on dissolution.

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FDA Meeting Discussion: Daiichi-Sankyo used Figures 3 and 4 (Appendix) to facilitate the discussion of FDA's preliminary response.

- Daiichi-Sankyo committed to include a copy of the drug substance specifications to be published in the USP Monograph for Amlodipine Besylate CTD.
- Daiichi-Sankyo committed to comply with the USP Monograph and add retention time as an identification test and to add the determination of heavy metals into the drug substance controls specifications and noted that all other test attributes, acceptance criteria and test methods are identical to the Ph. Eur. Monograph.
- Participants acknowledged and agreed that the compendial methods are considered validated, but that applicability to the drug product needed to be verified.
- Daiichi Sankyo committed to further evaluate FDA's recommendation that acceptance criteria for process and synthesis related impurities and particle size distribution for inclusion as drug substance (amlodipine besylate) controls.
- FDA recommended that specifications for all suppliers be the same, based on actual data and be consistent with the corresponding limits in the suppliers' Drug Master Files (DMF). A single set of specifications with supplier or material specific footnotes or notations where applicable should be reported in the CTD.

- 2.1 Does the Agency concur that the stability protocol agreed to verbally by FDA for primary stability batches submitted in the aforementioned amendments (*as described in the meeting package*) is sufficient for obtaining necessary stability data for CTD?
- 2.2 Does the Agency agree to accept the initial CTD with 9 months stability at the ICH conditions defined in the submitted (*as described in the meeting package*) stability study protocol?

FDA Preliminary Response: The stability protocol and initial CTD submission of 9 month stability data are acceptable as presented in the meeting package.

FDA Meeting Discussion: Daiichi-Sankyo acknowledged and agreed with FDA's recommendation.

- 3.1 Does the Agency agree to accept and use the updated stability data from the primary studies and the interim statistical analysis report in the determination of the assigned expiry dating period for the drug product?
- 3.2 Does the Agency agree that submission of this data and report (*as described in the meeting package*) does not constitute a major amendment necessitating an extension of the review clock?

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FDA Preliminary Response: Please confirm that the 4 month time referred to in the meeting package from the filing date is the date of initial submission to the FDA (stamp date). Stability data and statistical treatment can be submitted as an amendment to the NDA at any time during the review cycle. In accordance with the Good Review Management Principles Guidance (April, 2005), the quantity of data provided and the timing of the submission will determine if it will be reviewed within the first review cycle, or if the review clock would be modified.

FDA Meeting Discussion: Daiichi-Sankyo used Figure 5 (Appendix) to facilitate the discussion of FDA's preliminary response.

- Daiichi-Sankyo confirmed that a single amendment is projected to occur 4 months after CTD submission, and would contain stability data tables updated with 12 month data in the same format as originally submitted, with an interim statistical analytical report.
- Participants agreed that these data would be evaluated to support the assigned expiry dating.
- FDA confirmed that if the content of the update matches the proposal described in the meeting package and during the meeting discussion, this submission would not constitute a major amendment necessitating an extension of the review clock.

4. Does the Agency agree to the qualification strategy (*as described in the meeting package*) for degradation products?

FDA Preliminary Response: We find the approach acceptable as described in the meeting package. We recommend that you include the chemical name and structure for all degradation products.

FDA Meeting Discussion: Daiichi-Sankyo acknowledged and agreed with FDA's recommendation.

5. Does the Agency agree to this approach for the establishment of the proposed in vitro test methodology and specifications for the drug product?

FDA Preliminary Response: Paddle speed of 100 rpm is not recommended by FDA or USP since the discriminating ability of the dissolution test at this high paddle speed is very limited.

The dissolution data presented for formulation G shows that you are able to observe more than 80% dissolution for both olmesartan medoxomil and amlodipine besylate at pH 6.8 in 30 minutes at 50 rpm. In light of the dissolution data from formulation G and other formulations, your rationale for the proposed dissolution testing based on dissolution data from Olmetec 40 mg and Antacal 10 mg tablets together is not appropriate.

We recommend that you provide full dissolution profiles for the proposed marketed formulation using different media and speeds with both USP Apparatus 1 and 2.

FDA Meeting Discussion: Daiichi-Sankyo used Figures 6 - 9 (Appendix) to facilitate the discussion of FDA's preliminary response.

- Participants agreed that the 100 RPM paddle speed was not sufficiently discriminatory for submission.
- Daiichi-Sankyo indicated that the existing stability program (release to 6 months) includes dissolution results with 50 RPM and 100 RPM paddle speeds. Daiichi-Sankyo proposed that the stability program be modified to continue with dissolution testing at 50 RPM paddle speed, add 75 RPM paddle speed and discontinue the testing at 100 RPM paddle speed. FDA agreed to the proposal and stated that the dissolution methodology and specification for production batches would be determined during NDA review on the basis of dissolution data obtained from tests conducted at 50 and 75 rpm.

6. Does the Agency agree with the proposed approach for conformance to Ph. Eur. requirements for formulation excipient controls?

FDA Preliminary Response: In general, excipients which have not been harmonized between USP and Ph. Eur. should comply with the current USP monographs. However, Ph. Eur. monographs for excipients with equivalent or tighter acceptance criteria and test methods than USP monographs may be acceptable with adequate justification.

FDA Meeting Discussion: Daiichi-Sankyo acknowledged and agreed with FDA's recommendation. Daiichi-Sankyo committed that if not fully harmonized, the excipient controls will comply with EP/USP monographs.

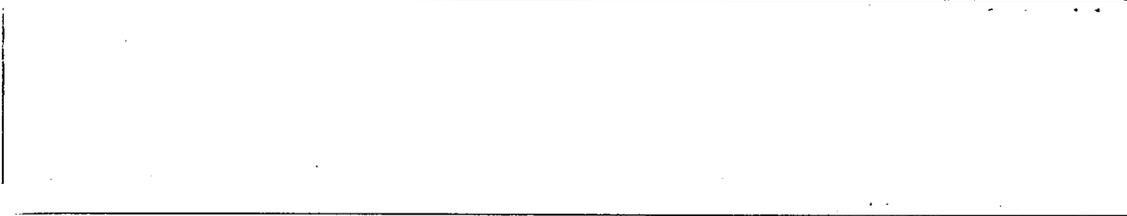
7. Is the approach of providing one authorized condensed English translation copy of the original executed batch record for a single drug product strength acceptable to the Agency?

FDA Preliminary Response: Please confirm that one English translation master batch record and one executed batch record from each dose strength will be submitted as described on page 56 of your meeting package.

FDA Meeting Discussion: Daiichi-Sankyo acknowledged and agreed with FDA's recommendation. Daiichi-Sankyo committed to provide one English translation of the master batch record and one narrative English summary of the executed batch record for each strength.

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Other FDA Comments:



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FDA Meeting Discussion: Daiichi-Sankyo used Figure 10 (Appendix) to facilitate the discussion of FDA's preliminary response.

- FDA recommended that Daiichi-Sankyo justify why is not an important particle size specification and would not have impact on the quality of the drug product
- Participants agreed that adequate justification needed to be provided in the CTD, with scientific discussion of the rationale of the particle size specifications and acceptance criteria based on the data.

b(4)

FDA Meeting Discussion: Daiichi-Sankyo used Figure 11 (Appendix) to facilitate the discussion of FDA's preliminary response.

- Daiichi-Sankyo proposed a 12 day duration thermal cycling study of three temperature cycles; each cycle would consist of 2 days at -20°C at ambient relative humidity followed by 2 days at 40°C at 75% relative humidity. Data for appearance, assay, related substances, mass of tables, water content and dissolution would be collected at initial and 12 days.
- Daiichi-Sankyo inquired about the possibility of application of bracketing some of the 6 strengths in this proposed program, and about the possibility of this proposed testing protocol as a Phase IV commitment.
- FDA indicated that this issue should be addressed during the NDA review, and not as a post-approval commitment. FDA indicated that further internal discussion was needed regarding the design of the experiments and the bracketing proposal. FDA committed to provide this feedback in a post-meeting comment appended to the meeting minutes.

FDA Post-Meeting Comment: Upon further deliberation and taking into consideration the properties of the approved monotherapy products, it was decided that shipping studies are not needed for this combination drug product.

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}

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

APPENDIX:

Figure 1

Key Discussion Points

- Question 1 –Amlodipine controls
- Question 3- Stability Update (12 months) Information and submission
- Question 5- Dissolution test method conditions
- Other FDA Comments 1. Drug substance PSD specifications
2. Bulk tablet shipping study



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Figure 2

Sponsor Updates to FDA Responses

- Question 2- Agreed
- Question 4- Agreed
- Question 6- Agreed; if not fully harmonized, excipient controls will comply with EP/USP monographs
- Question 7- Agreed; will provide one English Translation of the master batch record and one narrative English summary of executed batch record for each strength.

page 2



Figure 3

FDA Response 1 Amlodipine Besylate Controls

- Monograph announced in USP 30 Supplement 1 PF32(3)
 - Official April 2007
 - Difference from EP
- Addition of RT for identification
- Addition of heavy metals
- The additional tests will be incorporated into the drug substance controls
 - All other test attributes, acceptance criteria and test methods identical to EP
 - Compendial methods are considered validated

page 3

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Figure 4

FDA Response 1 cont'd.

1. Residual solvents limits will be based on actual data.
 - will be consistent with the corresponding limits in the suppliers DMFs

2. API from both suppliers meets the proposed PSD acceptance criteria.
 - In vitro dissolution test results on drug product manufactured from lots of drug substance from both suppliers demonstrated equivalency.

page 4



Figure 5

FDA Comments 3 Date and Content of Stability Update Information Amendment

- Submission: March 2007 (4 months after CTD submission FDA stamp date)
- Contents:
 - 9 months stability data tables updated with 12 months
(Presentation format of 12 months data will be same as for 9 months data)
 - Interim statistical analytical report
- Confirmation of sponsor question 3
 - Use of updated stability data to support the assigned expiry dating
 - Confirmation that this submission does not constitute a major amendment necessitating an extension of the review clock

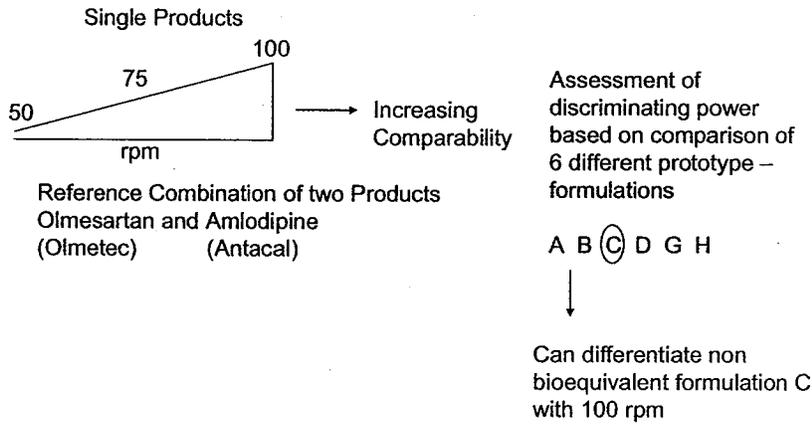
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Figure 6

**FDA Comments 5
 Dissolution Method**
 Development Rationale for 100 rpm



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Figure 7

FDA Comments 5 cont'd.

Alternate Approach 75 rpm	
Paddle Speed	Conforming to the guidelines for IR solid oral dosage forms
Possible specification (both actives)	Q= @30min /pH 6.8 media
Discriminatory power	Better than 100 rpm speed level

b(4)

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Figure 8

FDA Comment 5 cont'd. Method Development

Paddle (App. 2)

USP <1088> preferred for tablets

50 rpm

pH 1.2 4.5 6.8

100 rpm

pH 1.2 4.5 6.8

75 rpm

pH 6.8

(4.5) 1.2 to be completed with Formulation G

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Figure 9

FDA Comments 5 cont'd. Dissolution Method for ICH Stability Program

Registration batches	0 – 6 M 9 – 36 M	50 rpm and 100 rpm* 75 rpm
Production scale batches	0 – 36 M	75 rpm

*100 rpm not to be reported in the CTD

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Figure 10

Other FDA Comments 1
PSD range and acceptance criteria
Particle Size Specifications

Olmesartan medoxomil

Amlodipine Besylate

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Figure 11

Other FDA Comments 2
Proposed Shipping Study

Thermal cycling study

- 3 Cycles
 - Each cycle consists of two days at -20°C and two days at 40°C
- 12 Days Total
- Test at initial and 12 days
- Test for appearance, assay, related substances, mass, water content, and dissolution

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