

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200175

OTHER REVIEW(S)

NDA 200175 TRIBENZOR (olmesartan/amlodipine/HCTZ) Tablets
RHPM Overview
July 14, 2010

Sponsor: Daiichi-Sankyo
Type: 505(b)(2)/4S
Receipt Date: September 30, 2009
Goal Date: July 31, 2010

Action: Approval
Action Date: July 23, 2010

Background

This 505(b)(2) application was submitted on September 30, 2009. TRIBENZOR is a combination agent containing three previously-approved antihypertensive agents (olmesartan, amlodipine, and hydrochlorothiazide). The sponsor conducted multiple clinical and non-clinical trials to support approval. The main clinical trials conducted were a bioequivalence study comparing Daiichi formulations to approved formulations, and a ~2500 patient efficacy study comparing various dual combinations to the highest dose of the triple combination (40/10/25 mg). The clinical development program was conducted under IND 77651.

Division Director's Memo (7//10)

Reviewer: Norman Stockbridge, M.D., Ph.D.

Recommendation: Approval

Summary: This memo conveys the Division's decision to issue an Approval letter for Tribenzor for hypertension. This application has been the subject of reviews of CMC (Shiromani; 31 March and 16 July 2010), pharmacology/toxicology (Jagadeesh; 20 April 2010), clinical pharmacology (Kumi, Madabushi, and Liu; 28 June 2010), and medical and statistics (Gordon and Kong; 22 April 2010). There is a comprehensive CDTL memo (Karkowsky, 15 July 2010) with which I am largely in agreement.

CDTL Review (7/15/10)

Reviewer: Abraham Karkowsky, M.D., Ph.D.

Recommendation: Approval

Summary: Dr. Karkowsky's review indicates that the addition of a third drug to the each of the possible dual combinations resulted in a statistically significant reduction in both DBP and SBP ($p < 0.00$). He recommends labeling TRIBENZOR:

- As a product of convenience when it is substituted for the same dose of the individual components.
- As a reasonable alternative when a subject has been treated with the maximally tolerated or labeled doses of two components and still requires additional antihypertensive effects. Under the latter circumstance, a decision should be made whether alternative monotherapy or combination therapy would be preferable to adding a third drug to the ongoing combination.

Triple therapy appears much too aggressive to be used as initial therapy. Adverse events for the triple therapy are greater than those of the dual therapies and there seems no compelling reason to routinely expose subjects to the safety risks. There seems to be no credible scenario where more than one component of the triple combination should be increased at a time. It would seem that only the newly added component may require up-titration.

Adverse events and serious adverse events are increased during the time period subjects were on triple therapy compared to the dual therapies. Not surprisingly, hypotensive events (including vasodilatation events) were more prominent during treatment with triple therapy than with dual therapy. Renal dysfunction was also more common with triple therapy. The decrease in renal function was largely, but not completely, reversed after a reasonable post treatment washout.

Medical/Statistical Review (4/22/10)

Medical Reviewer: Maryann Gordon, M.D.

Statistical Reviewer: Fanhui Kong, Ph.D.

Recommendation: Approval

Summary: The primary medical and statistical reviewers of this application, pertaining to the use of the triple combination olmesartan medoxomil (OM), amlodipine besylate (AML) and hydrochlorothiazide (HCTZ) in the treatment of patients with hypertension, are recommending approval.

Clinical Pharmacology and Biopharmaceutics Review (6/28/10)

Reviewers: Robert Kumi, Ph.D.; Rajanikanth Madabushi, Ph.D.; Mehul Mehta, PhD.

Pharmacometrics Reviewers: Jiang Liu, Ph.D.; Pravin Jadhav, Ph.D.

Recommendation: Approval

Summary: The Office of Clinical Pharmacology (OCP) finds the clinical pharmacology and biopharmaceutics information submitted to NDA 200175 acceptable pending the inspection findings by the Division of Scientific Investigations (DSI).

Additionally, agreement must be reached between OCP and the applicant regarding labeling.

(b) (4)

. A statement indicating the dose-dependent increase in the blood pressure lowering effect of the triple combination products is more appropriate:

“All of the dose strengths of the triple combination are expected to provide superior blood pressure lowering effects compared to their respective mono and dual combination components. The order of the blood pressure lowering effects among the different dose strengths of the triple combination is expected to be 20/5/12.5 < 40/5/12.5 < (40/10/12.5 ≈ 40/5/25) < 40/10/25 [OM/AML/HCTZ].”

Pharmacology/Toxicology Review (4/20/10)

Reviewer: Gowra Jagadeesh, Ph.D.

Recommendation: Approval

Summary: Dr. Jagadeesh’s review indicates that there are no outstanding issues (beyond labeling recommendations) and the application can be approved from a pharmacology/toxicology standpoint.

Chemistry Review (3/31/10, 7/16/10)

Reviewer: Prafull Shiromani, Ph.D.

Recommendation: Approval

Summary: Dr. Shiromani’s 7/16/10 review indicates that there are no outstanding issues and that the application can be approved from a CMC standpoint.

Division of Scientific Investigations (DSI)

Overall Assessment and Recommendation: DSI inspected two clinical sites; Dr. David Ramstad, Chesapeake, VA, and Dr. Yekaterina Khronusova, Las Vegas, NV. Dr. Ramstad’s site was classified as NAI. Regulatory violations were noted at Dr. Khronusova’s site, but these violations were not likely to importantly impact data reliability. Thus the data are considered acceptable to support this application.

Pediatric Rule: The sponsor requested a waiver from conducting pediatric studies because TRIBENZOR is a combination antihypertensive agent and such agents are not widely used in pediatric patients. The Division agreed with the waiver request. The waiver was discussed at a June 2, 2010 PeRC meeting and the committed agreed a waiver is appropriate.

Labeling: Labeling was provided in the required PLR format. In addition to the review team, SEALD, DMEPA, DDMAC, and DRISK provided input on the labeling.

Advisory Committee: TRIBENZOR was not discussed at an Advisory Committee.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

RUSSELL FORTNEY
07/19/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 01, 2010

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Through: Mary Willy, PhD, Deputy Director
Division of Risk Management (DRISK)
Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Steve L. Morin, RN. BSN OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Tribenzor (olmesartan medoxomil, amlodipine
and hydrochlorothiazide) Tablets

Application
Type/Number: NDA 200-175

Applicant/sponsor: Daiichi Sankyo, Inc.

OSE RCM #: 2010-1265

1 INTRODUCTION

Daiichi Sankyo, Inc submitted an original 505 (b) (2) New Drug Application, NDA 200-175, for Tribenzor (olmesartan medoxomil, amlodipine and hydrochlorothiazide) Tablets on September 30, 2009. This application relies on the Agency's previous finding of safety and efficacy for information in NDA 21-286 for the Reference Listed Drugs, olmesartan medoxomil (Benicar®) for 5 mg, 20 mg, 40 mg oral tablets, in NDA 21-532 for Reference Listed Drugs, olmesartan medoxomil and hydrochlorothiazide (Benicar HCT®), and in NDA 22-100 for Reference Listed Drugs, amlodipine and olmesartan medoxomil (Azor®) sponsored by Daiichi Sankyo.

This review is written in response to a request by the Division of Cardiovascular and Renal Products (DCRP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Tribenzor (olmesartan medoxomil, amlodipine and hydrochlorothiazide) Tablets. Please let us know if DCRP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Tribenzor (olmesartan medoxomil, amlodipine and hydrochlorothiazide) Tablets Prescribing Information (PI) submitted September 30, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on June 16, 2010.
- Draft Tribenzor (olmesartan medoxomil, amlodipine and hydrochlorothiazide) Tablets Patient Package Insert (PPI) submitted on September 30, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on June 16, 2010.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- Incorporated language regarding cardiovascular outcomes based upon agreement with DCRP in relation to the DRISK review of the Coreg and Coreg CR PPI's, dated May 28, 2010, 2010, and further revised in the Complete Response letter dated June 10, 2010.
- Referenced the approved PPI for Exforge HCT (NDA 22-314) as a comparator.

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

STEVE L MORIN
07/01/2010
DRISK Final Review of Tribenzor PPI 07.01.10

MARY E WILLY
07/01/2010
I concur

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 28, 2010

TO: Russell Fortney, Regulatory Project Manager
Maryann Gordon, Medical Officer
Division of Cardiovascular and Renal Products

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 200-175

APPLICANT: Daiichi-Sankyo Pharma Development

DRUG: (b) (4) (olmesartan medoxomil + amlodipine +
hydrochlorothiazide)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of hypertension

CONSULTATION REQUEST DATE: December 7, 2009

DIVISION ACTION GOAL DATE: July 31, 2010

PDUFA DATE: July 31, 2010

I. BACKGROUND:

Daiichi-Sankyo submitted this NDA in support of the approval of a triple combination olmesartan medoxomil (OM) 40 mg + amlodipine 10 mg + hydrochlorothiazide (HCTZ) 25 mg as superior to its corresponding dual combinations in terms of blood pressure reductions.

One protocol was inspected in support of this application:

Protocol CS8635-A-U301: "A Randomized, Double-Blind, Parallel Group Study Evaluating the Efficacy and Safety of Co-Administration of a Triple Combination Therapy of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide in Subjects with Hypertension"

The primary objective of the study was: to demonstrate that the triple combination of OM 40 mg + AML 10 mg + HCTZ 25 mg is more efficacious in lowering seated diastolic blood pressure (SeDBP) than each of the corresponding dual components OM 40 mg + AML 10 mg, OM 40 mg + HCTZ 25 mg, after 12 weeks of treatment. The OM/AML/HCTZ combination is indicated in subjects whose blood pressure is not adequately controlled with OM/HCTZ or with OM/AML.

The planned duration of this study was 57 weeks with 52 weeks of treatment. This included a 3-week stabilization/washout period (Period I), a 12-week double-blind treatment period (Period II), a 40-week open-label treatment period (Period III) and a 2-week post-treatment follow-up period. The study enrolled 2492 subjects (~ 600 per treatment arm) at 317 sites in the U.S. The primary efficacy variable was the change from baseline in Seated Diastolic Blood Pressure (SeDBP) at Week 12 with the last observation carried forward (LOCF).

Dr. Khronusova and Dr. Ramstad's sites were selected for inspection using the Risk Based Site Selection tool. The primary driver in the risk assessment for each was high enrollment numbers. Dr. Khronusova had 37 INDS in COMIS with no prior inspections, and Dr. Ramstad had 13 INDS in COMIS with no prior inspections.

II. RESULTS (by Site):

Name of CI	Protocol #: and # of Subjects:	Inspection Date	Final Classification
David Ramstad, MD Site #111 700 N. Battlefield Blvd Chesapeake, VA 23320	CS8635-A-U301 80 subjects enrolled	January 27 - February 5, 2010	NAI
Yekaterina Khronusova, MD Advanced Biomedical Research of America 8420 South Eastern Las Vegas, Nevada 89123	CS8635-A-U301 65 subjects enrolled	March 10-19, 2010	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

1. David Ramstad, MD, 700 N. Battlefield Blvd, Chesapeake, VA 23320

- a. **What was inspected:** This site screened 116 subjects, and enrolled 80 subjects into the study. There were 36 screen failures, 2 subjects were terminated early, 2 subjects were withdrawn, 11 subjects were lost to follow up and 65 subjects completed the study.

During the inspection 20 subject files were reviewed (~ 30%). The records reviewed included source documents, medical records, laboratory reports, electrocardiograms, electronic case report forms (eCRFs), screening/enrollment logs, test article accountability records, study monitoring logs, IRB approvals and correspondence, correspondence with the CRO, protocol amendments, ICFs and media recruitment materials. The FDA investigator also reviewed and verified that informed consent forms for 28 subjects had been properly executed and signed. There were no limitations to the inspection.

- b. **General observations/commentary:** The FDA investigator reported the data as legible and well organized. The FDA investigator noted that most subjects were on blood pressure medications prior to enrollment and had to undergo a washout period prior to enrollment and randomization. While the FDA investigator identified a number of out-of-window visits for a few subjects, these protocol deviations were related to Dr. Ramstad's move to Chesapeake, VA, and the IRB was appropriately notified of these protocol violations. No Form FDA 483 was issued at this site.

The FDA investigator reported that Dr. Ramstad began enrolling subjects into this study in May 2008, while employed at Lakeview Medical Center, Suffolk, VA. Dr.

Ramstad was terminated without notice on August 27, 2008, and forced to relocate without warning in September 2008, to a location in Chesapeake, VA. According to the FDA investigator, Dr. Ramstad appeared to be a dedicated, outstanding physician, who had worked for Lakeview for 17 years. Dr. Ramstad stated that the reasons for his dismissal were related to a certain administrator, who he stated was receiving kickbacks, and did not like to be challenged. Apparently, several other physicians had been released about the same time. The FDA investigator stated that he did not identify any issues suggesting scientific misconduct by Dr. Ramstad.

- c. **Assessment of data integrity:** Although some out-of-window visits were noted as a minor deviation, these do not appear to affect the overall reliability of the data reported from this site for the study. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Yekaterina Khronusova, MD, Advanced Biomedical Research of America,
8420 South Eastern, Las Vegas, Nevada 89123

- a. **What was inspected:** At this site, 222 subjects were screened, 68 subjects were randomized, 32 subjects withdrew, and 36 subjects completed the study. The inspection reviewed records of 22 study participants, including all clinical study records, e-CRFs, clinic notes, the regulatory binder, IRB correspondence, laboratory results, and other study related documentation. Data in source records were compared to the data listings provided with the assignment.

The inspection reviewed the subject's pre-existing condition and all study related adverse events. The inspection reviewed new conditions or events that occurred since the previous visit, which had been documented in the clinic notes. The inspection reviewed concomitant medications reported in the subject's chart, drug storage facilities, and drug accountability records.

- b. **General observations/commentary:** A multi-part, 2 observational Form FDA 483 was issued at the end of this inspection, for: 1) investigation not conducted according with the signed statement of investigator; and 2) drug disposition records not adequate with respect to quantity and use by subjects. Dr. Khronusova responded in writing on March 26, 2010, to the inspectional observations. During review of 22 subject records, the following items were noted:

Item I. Failure to follow the protocol [21 CFR 312.60] Specifically:

- a. The protocol specified: the difference in mean SeSBP/SeDBP between two consecutive subject visits prior to randomization must be $\leq 20/10$ mmHg, or the subject is not eligible for the study.

The investigation found 2 subjects who did not meet this inclusion criteria: Subject 070-0144 had reported BP at Visit 1 of 180/114 mm Hg, and BP of 127/81 mm Hg at

Visit 2, or a diastolic BP difference of 33; and Subject 0070-0100 had BP 195/101 mm Hg at Visit 1 and 164/100 at Visit 2, or a systolic BP difference of 31. **For both subjects, the site obtained approval from the CRO for the subjects to continue in the study.** DSI does not consider this issue critical.

b. Protocol exclusion criteria #4 specified that subjects with a prior history of stroke or TIA will not be randomized in the study. The inspection found that Subject 0070-0013 had a history of TIA prior to randomization. **The site had obtained approval from the CRO to enroll the subject into the study.** DSI does not consider this issue critical.

c. Protocol exclusion criteria #5 specified that subjects could not be enrolled into the study if he/she had participated in another clinical trial within one month prior to screening. The inspection found that medical records for Subject 0070-0139, who was randomized on 9/17/2008, indicated this subject was enrolled in another study with a cardiologist, and was receiving medication from that study at the time of enrollment. DSI does not have exact dates for the timeframe of enrollment in the other study, but recommends that this subject be excluded from the analysis for this study.

d. Protocol exclusion criteria #20 prohibits inclusion of subjects on specific concomitant medications. The inspection found that Subject 0070-0168 was administered prednisone from 1/23-28/2009 and Subject 0070-149 was administered a cortisone injection for treatment of arthritis pain on 2/5/2009. **The site had been granted waivers from the CRO for including these subjects into the study.**

Item II: Investigational drug disposition records are not adequate with respect to quantity and use by subjects.

a. Review of study records indicated discrepancies between source documents and e-CRFs. For example, for Subject 0004, source records documented 15 tablets returned at Visit 16, whereas the e-CRF documented 7 tablets returned; Likewise, for Subject 0025, source documents recorded 13 tablets returned at Visit 16, whereas e-CRFs documented 12 tablets.

b. During Visit 16, Subject 0070-0001 was dispensed Study Kit #s AZOR 314665 and HCTZ 514040. These study kits were not returned for accountability, but were re-dispensed to the subject during Visit 17.

c. During Visit 15, pregnancy test was conducted for Subject 0070-0004; however, the kit's lot number and expiration date were not documented in the source document.

c. **Assessment of data integrity:** With the exception of Subject 0070-0139, who was enrolled in another cardiology study at the time of enrollment into CS8635-A-U301, no major regulatory violations were noted that would importantly impact study reliability, as the noted regulatory violations are considered isolated in nature. DSI considers the data from the site as acceptable in support of this application.

Note: Observations noted above with respect to the inspection of Dr. Khronusova are based on the Form FDA 483, and a preliminary inspectional summary report from the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigators were inspected in support of this application. No significant issues were identified during the inspection of Dr. Ramstad. Although regulatory violations were noted at Dr. Khronusova's site, the violations are considered isolated in nature and unlikely to importantly impact data reliability. Based on two inspections as summarized above, DSI considers the data reliable and may be used in support of the NDA.

Note: Observations noted above with respect to the inspection of Dr. Khronusova are based on the Form FDA 483, and a preliminary inspectional summary report; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

SHARON K GERSHON
07/02/2010

TEJASHRI S PUROHIT-SHETH
07/02/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

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

Date: June 21, 2010

To: Russell Fortney – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Zarna Patel – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Michael Sauers – Group Leader
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments
NDA 200175 Tribenzor (olmesartan medoxomil, amlodipine, hydrochlorothiazide)
Tablets**

DDMAC has reviewed the proposed product labeling (PI) for Tribenzor (olmesartan medoxomil, amlodipine, hydrochlorothiazide) tablets (Tribenzor), submitted for consult on April 22, 2010.

The following comments are provided using the updated proposed PI sent via email on June 3, 2010 by Russell Fortney. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

EMILY K BAKER
06/21/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 3, 2010

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Through: Melina Griffis, RPh, Team Leader
Denise Toyer, Pharm D, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Richard Abate, RPh, MS, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Tribenzor (Olmesartan Medoximil, Amlodipine, and Hydrochlorothiazide) Tablets 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, and 40 mg/10 mg/25 mg

Application Type/Number: NDA 200175

Applicant: Daiichi-Sankyo

OSE RCM #: 2010-392

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' evaluation of the proposed labels and labeling for Tribenzor (NDA 200175) submitted on March 30, 2010. We provide recommendations in Sections 3.1 and 3.2 with regards to the proposed product labels and labeling.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product labels and labeling submitted March 30, 2010 to identify vulnerabilities that could lead to medication errors. (See Appendices.)

3 CONCLUSIONS AND RECOMMENDATIONS

Our Labels and Labeling Risk Assessment indicates that the presentation of information in the labels and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval, and thus we provide recommendations in the following sections that aim at reducing the risk of medication errors.

3.1 COMMENTS TO THE DIVISION

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Nina Ton, project manager, at 301-796-1648.

We request the recommendations in Section 3.2 be communicated to the Applicant prior to the approval of this NDA.

3.1.1 General Comments

1. The established name as presented lacks the word "and." We recommend revising to read "Olmesartan Medoximil, Amlodipine, and Hydrochlorothiazide."
2. The presentation of the strength throughout the labeling requires the unit of measure (mg) for all active ingredients to be consistent with the presentation on the container labels and carton labeling. The strength should be presented as 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, and 40 mg/10 mg/25 mg.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1.2 Insert Labeling – Full Prescribing Information

3.1.2.1 Section 2 Dosage and Administration

The language for dosing of Tribenzor in replacement therapy is inconsistent between the Highlights section and the Full Prescribing Information. The statement for Replacement Therapy in Full Prescribing Information Section 2 reads, [REDACTED] (b) (4)

[REDACTED] The Highlights section states “Dosage may be increased..... usually by increasing one component at a time...” Therefore, to be consistent with the Highlight section, we recommend that the statement in the Dosage and Administration section be revised to [REDACTED] (b) (4)

3.2 COMMENTS TO THE APPLICANT

A. General Comments – for all container labels and carton labeling

1. Revise the presentation of the established name on the container labels and carton labeling so that it shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).
2. Remove the [REDACTED] (b) (4) between the proprietary name and the established name as “the ingredient information required by section 502(e) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter...” per 21 CFR 201.10(a).
3. Relocate the dosage form to appear after the active ingredient and before the presentation of the strength on professional sample blisters, container labels, and carton labeling. This is the customary presentation of information and provides for the ease of locating necessary information by healthcare providers and patients. For example:

Tradename
(Olmesartan Medoximil, Amlodipine, and Hydrochlorothiazide) Tablets
20 mg/5 mg*/12.5 mg
*each tablet contains 6.9 mg amlodipine besylate

B. Carton Labeling and Container Labels for 40 mg/10 mg/25 mg tablets

1. The color utilized to differentiate the 40 mg/10 mg/25 mg tablets [REDACTED] (b) (4)
[REDACTED] of the carton labeling and professional

sample blister cards, thus making the strengths more difficult to distinguish. Revised the color used for the presentation of the 40 mg/10 mg/25 mg strength to one not used in the product's trade dress yet still distinguishable from the colors used for the remaining strengths of this product.

- C. Container labels (30 count bottle and seven day sample bottle)
 - 1. As this is unit of use packaging, use child resistance closures to ensure compliance with the Poison Prevention Act.
- D. Container labels (90 count bottle)
 - 1. See Comment C1.
 - 2. The (b)(4) is inappropriately applied. As presented, the use of the (b)(4) compared to the established name. Remove the (b)(4). After removing the (b)(4) relocate the net quantity to the edge of the principle display panel similar to the net quantity presentation on the 30 count bottle and seven day sample bottle container labels.
- E. Carton Labeling (Hospital Unit-dose 10x10 blister)
 - 1. The prominence of (b)(4) Remove this prominent field to improve the ability of users to better distinguish the product strengths.
- F. Unit Dose Blister (cards of 10 tablets)
 - 1. Revise the presentation of the information to be consistent with Comment A3 but not to include the statement describing the specific amount of salt for amlodipine besylate.
 - 2. Remove the strengths from the presentation of the established name as this is redundant information on a small label with limited space.
 - 3. Revise and provide additional methods to distinguish the strengths 20 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg, and 40 mg/5 mg/25 mg. The small font size on the unit dose blister in combination with color fonts used makes it difficult to distinguish these strengths and increases the likelihood of these strengths being confused. Additional distinguishing methods (i.e., highlighting, boxing, outlining, color bars, etc) should be incorporated into these labels.
- G. Professional Sample Carton Labeling
 - 1. Remove the prominent (b)(4) per Comment E1.
- H. Professional Sample Blister (cards of seven tablets)
 - 1. Add the statement "Each tablet contains" to the back of the blister card to include all three active ingredients and their respective strengths. In

addition, place this information so that it will be legible after tablets have been removed.

2. Remove the statement “Tradename 7-Day Sample” as this information detracts from the prominence of the product information on the principle display panel and is redundant.
 3. Remove the prominent purple field per Comment E1.
- I. Alternate Sample Blister (card of seven tablets)
1. Include a statement “Each tablet contains” which describes all the three active ingredients and their respective strengths.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

RICHARD A ABATE
06/03/2010

MELINA N GRIFFIS
06/03/2010

DENISE P TOYER
06/04/2010

CAROL A HOLQUIST
06/04/2010

Request for Clinical Inspections

Date: 12/7/2009

To: Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Jean Mulinde, M.D., Acting Team Leader GCP2
Sharon Gershon
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Maryann Gordon/Division of Cardiovascular and Renal Products:

From: Russell Fortney:

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA 200175

Daiichi-Sankyo (Regulatory Contact: Manini Patel)

Phone: 732-590-4319

Email: mpatel2@dsus.com

Drug Proprietary Name: (b) (4) (proposed name)

NME or Original BLA: This is not an NME

Review Priority: Standard

Study Population includes < 17 years of age: No

Is this for Pediatric Exclusivity? No

Proposed New Indications(s): Treatment of hypertension

PDUFA: July 31, 2010

Action Goal Date: July 31, 2010

Inspection Summary Goal Date: May 31, 2010

Advisory Committee Meeting Date: N/A

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. To be generated automatically

Site# (Name, Address, Phone Number, Fax Number, E-mail)	Protocol ID	Number of Subjects	Indication
<p>David Ramstad, MD 700 N. Battlefield Blvd, Suite B Chesapeake, VA 23320</p> <p>Phone # 757-842-4560 Fax# 757-842-4562 Email address: davidramstad@cox.net</p>			
<p>Yekaterina Khronusova, MD Advanced Biomedical Research of America 8420 South Eastern Avenue, Suite 102 Las Vegas, NV 89123</p> <p>Phone # 702-898-2088 Fax# 702-898-2013 Email address: abratrials@prodigy.net</p>			

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
- *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
- *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

RUSSELL FORTNEY
12/09/2009

MARYANN GORDON
12/09/2009

SHARI L TARGUM
12/11/2009

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 200-175
APPLICANT	Daiichi Sankyo, Incorporated
DRUG NAME	TRIBENZOR (olmesartan medoxomil, amlodipine, and hydrochlorothiazide)
SUBMISSION DATE	September 30, 2009
SEALD REVIEW DATE	June 21, 2010
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

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/s/

DEBRA C BEITZELL
06/21/2010
SEALD comments sent to DCRP on 6/21/10

LAURIE B BURKE
06/21/2010