

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-401**

**OTHER REVIEW(S)**



**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: October 1, 2009

To: Norman Stockbridge, M.D., Division Director  
**Division of Cardiovascular and Renal Products (DCRP)**

Through: Claudia Karwoski, PharmD, Division Director  
**Division of Risk Management (DRISK)**  
LaShawn Griffiths, MSHS-PH, BSN, RN, Acting Team Leader  
**Division of Risk Management (DRISK)**

From: Barbara Fuller, RN, MSN, CWOCN  
Patient Product Information Reviewer  
**Division of Risk Management (DRISK)**

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

Drug Name(s): Twynsta (telemisartan/amlodipine)Tablets

Application Type/Number: NDA 22-401

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2009-382

## **1 INTRODUCTION**

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 for Twynsta (telmisartan/amlodipine) 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 Twynsta (telmisartan/amlodipine) Tablets Prescribing Information (PI) submitted 12/18/2008 and revised by the Review Division throughout the current review cycle.
- Draft Twynsta (telmisartan/amlodipine) Tablets Patient Package Insert (PPI) submitted on 12/18/2008.

## **3 RESULTS OF REVIEW**

In our review of the PPI, we have:

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

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.

(F) 16 pages withheld immediately following this page as b(4) TS Draft labeling

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/s/

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ZARNA PATEL  
09/28/2009

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

Memorandum

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

**Date:** September 28, 2009

**To:** Quynh Nguyen  
Regulatory Project Manager  
Division of Cardiovascular and Renal Products (DCRP)

**From:** Michael Sauers, Regulatory Review Officer  
Zarna Patel, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** **TWYNSTA (telmisartan/amlodipine) Tablets**  
NDA 22-041  
Comments on draft product labeling

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DDMAC has reviewed the proposed product labeling (Package Insert (PI) and Patient Package Insert (PPI)), submitted for consult to DDMAC on December 18, 2008, for TWYNSTA (telmisartan/amlodipine) Tablets.

Our comments are based on the proposed labeling circulated to the review team on September 17, 2009. DDMAC's comments are provided directly in the attached document (see below).

Thank you for your consult.

If you have any questions on the comments for the PI, please contact Michael Sauers at 301.796.1035 or [michael.sauers@fda.hhs.gov](mailto:michael.sauers@fda.hhs.gov).

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

**28 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)**

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/s/  
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ZARNA PATEL  
09/28/2009

**MEMORANDUM**

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

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DATE: September 11, 2009

TO: Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products

FROM: Hyojong Kwon, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Mart K. Yan 9/11/09  
Associate Director - Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-401, Tywnsta  
(telmisartan /amlodipine) 40mg/5mg and 80mg/10mg  
tablets, Sponsored by Boehringer Ingelheim  
Pharmaceuticals, Inc.

At the request of the Division of Cardiovascular and Renal Products (DCRP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

**Study 1235.3:** An open-label, randomised, single-dose, two-period crossover bioequivalence study of 40 mg telmisartan/5 mg amlodipine fixed dose combination (Test formulation from Boehringer Ingelheim) compared with its monocomponents, Telmisartan 40mg tablet (Micardis®) and amlodipine 5 mg tablet (Norvasc®) in healthy male and female volunteers.

**Study 1235.4:** An open-label, randomized, single-dose, two-period crossover bioequivalence study of 80 mg telmisartan/10 mg amlodipine fixed dose combination (Test formulation from Boehringer Ingelheim) compared with its monocomponents, Telmisartan 80mg tablet (Micardis®) and amlodipine 10 mg tablet (Norvasc®) in healthy male and female volunteers.

Page 2 of 9-NDA 22-401, Tywnsta (telmisartan/amlodipine) 40mg/5mg and 80mg/10mg tablets

The clinical portions of Studies 1235.3 and 1235.4 were conducted at (b) (4) and Boehringer Ingelheim (BI) Pharma (Biberach, Germany), respectively. (b) (4) determined plasma concentrations of telmisartan for Study 1235.4 with an HPLC assay. The inspection at (b) (4) was waived by DSI (See the Attachment 1). BI Pharma (Germany) determined plasma concentrations of telmisartan for Study 1235.3 with ELISA method.

Following the inspections (8/10-8/14/2009 at CRS, 8/17-8/21/2009 at BI Pharma), a Form FDA 483 was issued for analytical portion at BI Pharma (Attachment 2) but there was no significant clinical issue identified. Our evaluation of the significant findings at the analytical site is as follows:

**Clinical Site:** 1. (b) (4)  
(b) (4)  
2. **Boehringer Ingelheim Pharma GmbH &Co.KG, Biberach, Germany.**

**Study 1235.3 and 1235.4**

No 483 observation

**Analytical Site: **Boehringer Ingelheim Pharma GmbH &Co.KG, Biberach, Germany****

**Study 1235.3**

1. **Failure to include adequate number of quality controls (QCs) in each 96-well microtiter plate to adequately monitor the assay performance of each plate.**

- **For example, each microtiter plate in a multi-plate batch had 1 set of standard calibrators but only three QC samples (one Low, one Mid, and one High QCs). The individual plate does not have enough QCs to accept or reject the data generated from the plate.**

Each microtiter plate (MTP) has up to 96 samples including a 7-points standard curve (a set of 7 standard calibrators) but only 1 set of QCs (low, mid, high). The firm prepared 10-MTP per batch but each MTP performed as a stand-alone batch by evaluating each standard curve and QCs of individual MTP. In light of the large number of samples in

each plate, there should have been 2 sets of QCs (2 low, 2 mid, 2 high) in each MTP to adequately monitor the run performance of each plate as a stand-alone batch.

There were 4 MTP rejected due to failing to meet acceptance criteria for standard calibrators. The firm re-assayed these samples to be reported (see the table below).

MTP	Samples
P480 005	All samples of S3V2
P480 131 (single-MTP batch, repeat of 480 005)	All samples of S3V2
P480 148	All samples of S74V2
P480 151	All samples of S75V3

(S:Subject, V:Visit)

In the firm's data analysis, they used an individual standard curve to evaluate QCs and unknowns on each MTP. Because the inadequate number of QCs on each MTP requires that acceptance of the QCs be evaluated for the batch as a whole, the firm should calculate one standard curve using all the calibrators from individual MTPs for each multi-plate batch and use this standard curve to evaluate the acceptability of QCs and plate-to-plate variability of calibrators for that batch.

**2. Failure to fully document and accurately report study procedure/data to ensure the integrity of study conduct.**

- For example,

(1) Not all re-assayed samples were identified in the final report.

(2) Two comparisons of '10-fold concentration calibrators to pre-diluted calibrators'

(GL0107C2/GL0107C1 and GL0107C5/GL0107C3) were evaluated but only GL0107C5/GL0107C3 was included in the report.

(3) Validation study period was reported as December, 2006-February, 2007, but the validation study includes samples analyzed in November, 2006.

The samples from 4 failed MTPs were not identified and reported as re-assayed samples in the final report. The firm also did not include all the experiments conducted during validation in the validation study report.

**3. Failure to follow the archiving procedure/SOP for source documents/data.**

**- For example, the archived hard-copy of the validation study did not include complete records of audit-trail.**

The firm should follow adequate archiving procedure to protect raw data/records/documents for accuracy and integrity of the study.

**Conclusion:**

Following our evaluation of the inspectional findings, DSI recommends that the firm (BI pharma) should be asked to generate one standard curve for each multi-microtiter plate (MTP) batch using all the calibrators in the batch. This standard curve should be used to evaluate the acceptability of QCs and plate-to-plate variability of calibrators in that batch to ensure accuracy of the data in Study 1235.3 (see Form 483-Item 1 above). The re-analysis results for all MTP batches should be submitted for evaluation.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

 9/11/2009  
Hyojong (Hue) Kwon, Ph.D.

**Final Classification:**

VAI-Boehringer Ingelheim Pharmaceuticals, Biberach, Germany

(b) (4)  

Page 5 of 9-NDA 22-401, Tywnsta (telmisartan/amlodipine)  
40mg/5mg and 80mg/10mg tablets

CC:

HFD-45/RF

CDER DSI PM TRACK

HFD-48/Kwon/Rivera-Lopez/CF

OND/DCRP/Nguyen

OCP/DCRP/Younis

HFR-NE1538/Brown

Draft:HK 09/02/09

Edit:JAK 09/08/09, MKY 09/11/09

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FACTS: (b)(4)

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/s/

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HYOJONG KWON

09/11/2009

Dr. Martin Yau (acting for Dr. Viswanathan) signed the paper copy on 9/11/2009.

**MEMORANDUM**

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

**DATE:** May 26, 2009

**TO:** Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products

**FROM:** CT. Viswanathan, Ph.D. *CTV 6/2/09*  
Associate Director - Bioequivalence  
Division of Scientific Investigations

**SUBJECT:** Recommendation to accept bioanalytical data from NDA 22-401 for review without onsite inspection

The Division of Scientific Investigations (DSI) recently received a request to audit the clinical and analytical portions of the following bioequivalence studies supporting NDA 22-401 (Tywnsta, telmisartan/amlodipine 40mg/5mg & 80mg/10mg tablets):

**Study 1235.3:** An open-label, randomised, single-dose, two-period crossover bioequivalence study of 40 mg telmisartan/ 5 mg amlodipine fixed dose combination (Test formulation from Boehringer Ingelheim) compared with its monocomponents, Telmisartan 40mg tablet (Micardis®) and amlodipine 5 mg tablet (Norvasc®) in healthy male and female volunteers

**Study 1235.4:** An open-label, randomized, single-dose, two-period crossover bioequivalence study of 80 mg telmisartan/10 mg amlodipine fixed dose combination (Test formulation from Boehringer Ingelheim) compared with its monocomponents, Telmisartan 80mg tablet (Micardis®) and amlodipine 10 mg tablet (Norvasc®) in healthy male and female volunteers

The clinical portions of Studies 1235.3 and 1235.4 were conducted at (b) (4) and Boehringer Ingelheim Pharma (Biberach, Germany), respectively. Plasma concentrations of amlodipine for both studies were determined at Nippon Boehringer Ingelheim in Japan. Boehringer Ingelheim Pharma (Germany) determined plasma concentrations of telmisartan for Study 1235.3 with an ELISA method. (b) (4)

(b) (4) determined plasma concentrations of telmisartan for Study 1235.4 with an HPLC assay.

Since DSI is looking for ways to optimize and prioritize our resources to work effectively with the review operations, and implement risk-based decisions when appropriate, we recommend at this time that the analytical portion of Study 1235.4 conducted at (b) (4) be accepted for your review without onsite inspection due to the following reasons:

- 1) (b) (4) was inspected twice since early 2008, with direct participation by DSI staff. We audited RIA and GC/MS bioanalytical methods and bioequivalence data for studies supporting the following applications:

March 2008, NDA 21-795 desmopressin acetate tablets

March 2009, NDA 22-446 norethindrone acetate/ethinyl estradiol chewable tablets

- 2) Form 483 was issued following these inspections. However, the findings of these inspections did not impact on the approvability of the applications.
- 3) During our inspections, we found that personnel from (b) (4) were highly qualified and keen on improving procedures where necessary.

Please note that our recommendation that the bioanalytical portion of Study 1235.4 conducted at (b) (4) (plasma concentrations of telmisartan) accepted without onsite inspection does not preclude future onsite audits at (b) (4), as we deem necessary.

Please note that DSI has no inspectional history for the other sites in Germany (b) (4) and Boehringer Ingelheim Pharma in Biberach) and Nippon Boehringer Ingelheim in Japan. We have initiated the inspection process for these sites and will provide our evaluation to you once the inspections are completed and we review the inspection reports.

If you have any questions or concerns, please contact me at (301) 796-3394.

cc: DFS

DSI/Viswanathan/Rivera-Lopez/CF

OND/DCRP/Nguyen

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/s/

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Carol Rivera-Lopez

6/5/2009 11:58:17 AM

PHARMACOLOGIST

Dr. Viswanathan signed the paper copy on 6/2/09.



**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 18, 2009

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

Through: Laura Pincock, RPh, PharmD, Acting Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Diane C. Smith, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Twynsta (Telmisartan and Amlodipine) Tablets  
40 mg/5 mg, 40 mg/10 mg, 80 mg/5 mg and  
80 mg/10 mg

Application Type/Number: NDA 22-401

Applicant/sponsor: Boehringer-Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2009-379

## **1 MATERIALS REVIEWED**

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode Effects and Analysis in our evaluation of the labels and labeling submitted as part of the March 4, 2009, submission. (See Appendices A through G).

## **2 RECOMMENDATIONS**

Our evaluation noted areas where information on the labels and labeling can be improved to minimize the potential for medication errors. We provided recommendations on the blister labels and carton labeling in Section 2.1 Comments to the Applicant. We request the following recommendations in Section 2.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Janet Anderson at 301-796-1332.

### **2.1 COMMENTS TO THE APPLICANT**

#### **A. General Comments**

1. Ensure that the established name is 1/2 the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. The dosage form of Twynsta (tablets) should be adjacent to the established name on all labels and labeling as follows:

Twynsta  
(Amlodipine and Telmisartan) Tablets

#### **B. Blister Label**

1. Revise the blister labels to provide for more adequate visual differentiation between strengths. As currently presented, the blister labels look identical and make it very difficult to readily identify the different product strengths. Differentiate the product strengths on the blister labels by using contrasting color, boxing, or some other means.
2. The Applicant's name and graphic are large and takes up unnecessary space. Decrease the size of the Applicant's name and graphic, as it is more prominent than the most important information on the label such as the proprietary name, established name, strength, and instructions for removing the tablet from the blister.
3. The blister package is considered the immediate container for each tablet and therefore is required to have a bar code which contains the applicable National Drug Code (NDC) number. Include the product bar code on each tablet blister label as required by 21 CFR 201.25(c)(1).

C. Carton Labeling

As currently presented, the 40 mg/10 mg and 80 mg/5 mg carton labeling look almost identical when compared side-by-side. We acknowledge the use of different color blocking with the different strengths, however, the overall trade dress blue/gray colors still makes the labels look similar. Change the color in the color blocks (i.e., grey for 40 mg/10 mg and blue for 80 mg/5 mg) of the two strengths to colors that do not overlap and are different than the colors in the trade dress.

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Labeling

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Diane Smith  
6/18/2009 03:18:01 PM  
DRUG SAFETY OFFICE REVIEWER

Laura Pincock  
6/18/2009 04:01:02 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
6/18/2009 04:05:37 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
6/18/2009 04:20:18 PM  
DRUG SAFETY OFFICE REVIEWER

**RHPM Overview – AP action**  
**NDA 22-401**  
**Twynsta (telmisartan/amlodipine) Tablets**  
**40/5, 40/10, 80/5, 80/10 mg**

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.  
Classification: Standard  
Submission Date: December 18, 2008  
Receipt Date: December 18, 2008  
User Fee Goal Date: October 18, 2009

**Background**

This original NDA provides for the use of Twynsta (telmisartan/amlodipine besylate) Tablets for the treatment of hypertension, including as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. The NDA was submitted pursuant to section 505(b)(2) and contains full study reports of the safety and efficacy of the combination drug product. The sponsor is proposing the following 4 dosage strengths: 40/5, 40/10, 80/5, 80/10 mg.

Reference is made to the non-clinical data of Norvasc (amlodipine) and Micardis (telmisartan) as approved in their respective labels. No additional non-clinical safety data in support of the fixed dose combination was provided, as agreed to during the Pre-NDA Meeting Preliminary Responses dated June 3, 2008.

In support of approval, the submission includes quality, clinical pharmacology, and clinical/statistical data. The clinical development program included one pivotal Phase 3 study and other supportive studies, 2 bioequivalence studies, 2 drug-drug interaction studies, and a food effect study.

The pivotal trial (Study 1235.1) was an 8-week, 4x4, placebo-controlled factorial design study, which included 3 strengths each of telmisartan and amlodipine. The study randomized and treated a total of 1461 patients with Stage 1 and Stage 2 hypertension. According to the sponsor, results showed clinically and statistically significant reductions in seated trough cuff DPB and SBP for the fixed dose combination compared to the monotherapy components and placebo.

Draft labeling for the carton and container, PI, and Patient PI was submitted in SPL and PLR format.

The sponsor is requesting a full waiver from the pediatric requirement.

The NDA is fully electronic in the EDR. A waiver allowing the sponsor to submit electronically but not in eCTD format was granted by OBPS, but in general the submission has been formatted as suggested in the eCTD guidance.

**Cross-Discipline Team Leader Review**

In his 9-17-09 review, Dr. Marciniak wrote the following:

13.1. Recommended regulatory action

I recommend Twynsta be approved for the treatment of hypertension in adults. This dual combination produced greater reductions in blood pressure than the monotherapies. The adverse event profile is similar to those of the monotherapies.

**Clinical Review**

In her 9-9-09 review, Dr. Blank's review states the following:

Pivotal trial 1235.1 and other supportive phase 3 and 4 trials submitted in NDA 22401, including

the ONTARGET trial (Mann et al, Lancet 2008 Aug 16; 372:547-53), demonstrate that Twynsta is safe and effective and is appropriate to use as a combination antihypertensive therapy drug for patients that are uncontrolled on monotherapy as well as a first line therapy for patients that are likely to require combination antihypertensive therapy.

The primary efficacy endpoint, a demonstration of superiority of highest marketed doses of the key combinations of telmisartan (T) and amlodipine (A) (T40mg + A5mg, T40mg + A10mg, T80mg + A5mg and T80mg + A10mg) over the individual monotherapies in lowering seated trough diastolic blood pressure (DBP), was met ( $p < 0.0001$ ) in trial 1235.1. Additionally, there were no compelling safety issues. In fact, the dose-limiting side effect of peripheral edema caused by amlodipine 10 mg was substantially less with the co-administration of telmisartan.

#### **Statistical Review**

In her 8-31-09 review, Dr. Liu wrote the following:

The study showed that the combination therapy of telmisartan plus amlodipine is more effective than either telmisartan or amlodipine in lowering seated trough cuff DBP in patients with Stage I or II hypertension, as well as in patients with moderate or severe hypertension. The study also seems to support the combination therapy for use as an initial therapy indication in patients with higher blood pressure baselines.

#### **Clinical Pharmacology Review**

In his 5-8-09 review, Dr. Younis wrote the following:

The Office of Clinical Pharmacology (OCP) has reviewed Original NDA 22-401 for Twynsta Tablets.

*Clinical Pharmacology:* OCP finds the clinical pharmacology and biopharmaceutical information submitted under NDA 22-401 acceptable, provided the audit reports from the Division of Scientific Investigations for the pivotal bioequivalence studies No. 1235.3 and 1235.4 are satisfactory. There are no Phase IV commitments.

*Labeling:* The proposed labeling does not include information for the effect that food has on telmisartan's C<sub>max</sub> (60% decrease). Therefore, sections 2.1 (Dosage and Administration) and 12.3 (Pharmacokinetics) of the proposed labeling should be revised as appropriate.

#### **Pharmacology review**

In his 3-26-09 review, Dr. Jagadeesh recommended that the NDA was "Approvable" and wrote the following:

The sponsor has not performed pharmacology, ADME or toxicology studies for the combination product. Nonclinical studies of the individual active components of the combination product are summarized in the pharmacology reviews of Boehringer Ingelheim's Micardis tablets (NDA 20850) and Pfizer's Norvasc tablets (NDA 19787).

#### **Quality reviews**

In his memo dated 10-14-09, Dr. Claffey wrote the following:

At the completion of CMC Review #1 for NDA 22-401 an approval recommendation was made pending the receipt of acceptable recommendations from the Office of Compliance (manufacturing sites), the Environmental Assessment reviewer (Raanan Bloom, PhD) and the ONDQA Biopharmaceutics reviewer (Tien-Mien Chen, PhD). At this time an acceptable recommendations have been made by each of these parties:

- Raanan Bloom, FONSI 8 SEP 2009 and 11 SEP 2009
- Office of Compliance, overall acceptable, E Johnson 1 OCT 2009 (Attachment 2)
- Tien-Mien Chen, PhD , approval recommendation (6 OCT 2009) with a post approval commitment by the applicant to study the feasibility of making changes to the dissolution specification of both telmisartan and amlodipine within 12 months of the action letter.

A recommendation was also made to add a statement to the carton labeling to indicate the strength of amlodipine in terms of its salt (labeled strength is in terms of the free base). It was agreed to allow the applicant to add this information at next carton label printing (email 25 SEP 2009 through PM with concurrence by Ramesh Sood via email 28 SEP 2009). The applicant states that the revised cartons will “enter the market from February 2010 onwards” (email to Quynh Nguyen, 25 SEP 2009). Mockups of the carton labels were provided in the 6 OCT 2009 (LC) amendment (Attachment 1). The revisions appear adequate from a CMC perspective – the PM was advised to obtain DMEPA concurrence on the proposed changes.

See also Dr. Ramesh Sood’s “Summary Basis for Recommended Action” dated 10-14-09, and Dr. Tien-Mien Chen’s Addendum to ONDQA Biopharmaceutics Review dated 10-5-09.

Note: As discussed and agreed with the Division of Pre-Marketing Assessment I, Office of New Drug Quality Assessment in a teleconference held on October 2, 2009, the following postmarketing commitment was agreed upon with the sponsor, as submitted to the NDA on 10-6-09:

1. Dissolution specification for telmisartan will remain at Q=(b) at 30 minutes. Within one year of NDA approval, Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) commits to change the dissolution specification for telmisartan to Q=(b) at 20 minutes unless BIPI submits data within this time period to show that the change is not supported.

2. For amlodipine, BIPI commits to generate the necessary data post approval to determine if the phosphate buffer pH 6.8 method is appropriate for the product. BIPI will collect stability data on the primary stability batches at 36 months as well as the ongoing stability for the first three production batches at 18 months per the post approval stability commitment, using both the dissolution media 0.01 N HCl at pH 2 and phosphate buffer at pH 6.8. Within one year post approval, BIPI will provide FDA with the data and an assessment as to whether the testing conditions using phosphate buffer pH 6.8 are appropriate for determination of amlodipine dissolution in telmisartan/amlodipine tablets. Should the dissolution method using the phosphate buffer at pH 6.8 be deemed suitable, an appropriate specification will be presented along with justification for the acceptance criteria.

#### **Environmental Assessment**

The sponsor submitted an Environmental Assessment (EA) pursuant to 21 CFR Part 25, which was found to be acceptable. See OPS reviews dated 9-4-09 (EA review) and 3-5-09 (FONSI).

#### **EER Report**

The Office of Compliance provided on 10-1-09 an overall recommendation of “Acceptable” for the manufacturing sites inspected. See Quality reviews.

#### **Safety Update**

See page 91 of Dr. Blank’s Medical Review dated 9-9-09.

#### **Financial Disclosure**

See page 20 of Dr. Blank’s Medical Review dated 9-9-09.

## **Division of Scientific Investigations**

### Clinical

The Division did not request an audit of the sites for the pivotal clinical study 1235.1 because both drugs are approved and there are a large number of sites, none of which accounted for a significant proportion of the patients.

### Bioequivalence

See Clinical Pharmacology Review section above regarding DSI inspections of the bioequivalence studies.

In their Memo signed on 6-5-09, DSI recommended the following:

Since DSI is looking for ways to optimize and prioritize our resources to work effectively with the review operations, and implement risk-based decisions when appropriate, we recommend at this time that the analytical portion of Study 1235.4 conducted at [REDACTED] (b) (4) be accepted for your review without onsite inspection...

In their Memo signed on 9-11-09, DSI concluded the following:

Following our evaluation of the inspectional findings, DSI recommends that the firm (BI pharma) should be asked to generate one standard curve for each multi-microtiter plate (MTP) batch using all the calibrators in the batch. This standard curve should be used to evaluate the acceptability of QCs and plate-to-plate variability of calibrators in that batch to ensure accuracy of the data in Study 1235.3 (see Form 4 S 3- Item 1 above). The re-analysis results for all MTP batches should be submitted for evaluation.

Note: In an email dated 9-14-09 regarding the above DSI memo dated 9-11-09, Dr. Younis wrote:

I do not think it is problem: during the analysis of study 1235.3 subject's plasma samples the precision of the quality control samples was  $\leq 6.8\%$  and the accuracy was  $-8.4\% - 0.3\%$ , this is far away from the 15% acceptance limit and I do not believe redoing the analysis as DSI suggested will change the results that much.

Dr. Stockbridge concurred with Dr. Younis' above response in an email dated 9-14-09.

Note: The Division had decided on 9-3-09 to cancel the DSI inspection request at the Nippon Boehringer Ingelheim site in Japan, which was scheduled for the week of October 11, 2009. However, per an email from Dr. CT Viswanathan of DSI on 9-3-09, DSI had already arranged the inspection for the Nippon Boehringer Ingelheim site. Since it was a new site for Bioequivalence work, DSI would go ahead with the inspection to assess compliance for own their records and would provide the Division with their findings anyway.

## **Pediatrics**

The sponsor requested a waiver from the pediatric requirement and the Division agreed.

A PeRC Committee meeting was held on 9-9-09 and the PeRC agreed with the Division to grant a full pediatric waiver for the following reasons:

The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

**Justification:** Twynsta is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not treated with combination antihypertensives (supported by **The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents**, *Pediatrics* 2004;

114;555-576).

**Labeling**

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

DDMAC provided comments on the proposed PI and PPI in a review dated 9-28-09.

DMEPA concluded that the proposed proprietary name "Twynsta" was acceptable in their reviews dated 9-16-09 (final) and 5-4-09 (original). Comments on the proposed container and carton labeling were provided in a review dated 6-18-09.

DRISK provided comments on the proposed PPI in a review dated 10-1-09.

The sponsor submitted revised carton and container labeling dated 7-10-09 and 10-6-09, which was acceptable except for the following minor change: the sponsor agreed at the time of next printing to revise the outer cartons for all strengths to add a statement with the amount of amlodipine besylate present and add an asterisk next to the strength and statement. This change will be reported in their next Annual Report. Labeling discussions were held with the sponsor on 10-14-09 during which time the revised PI and PPI labeling text was agreed upon as well as the minor change to the outer carton.

**Pre-Approval Safety Conference**

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

**User Fee**

The user fee for this application was paid in full (User Fee ID# PD3008825).

**505(b)(2) Clearance**

Per a 9-29-09 email from Beth Duvall-Miller, this NDA is cleared for action from a 505(b)(2) perspective.

**CSO Summary**

An Approval (AP) Letter based on the agreed-upon labeling text will be drafted for Dr. Stockbridge's signature. The AP Letter will include comments to the sponsor as noted in the Quality reviews section for the postmarketing commitment.

Quynh Nguyen, Pharm.D.  
Regulatory Health Project Manager  
10-16-09

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22401

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ORIG-1

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BOEHRINGER  
INGELHEIM  
PHARMACEUTICA  
LS INC

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TELMISARTAN/AMLODIPINE  
FIXED DOSE COM TB

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/s/  
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QUYNH M NGUYEN  
10/16/2009