

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-401**

**CHEMISTRY REVIEW(S)**

**Twynista**  
**(telemisartan/amlodipine) tablets**  
**NDA 22-401**

**Summary Basis for Recommended Action**  
**From Chemistry, Manufacturing, and Controls**

**Applicant:** Boehringer Ingelheim Pharmaceuticals  
Ridgefield, CT 06877

**Indication:** Indicated for the treatment of hypertension.

**Presentation:** Twynista (telemisartan/amlodipine) tablets are available in 40/5 mg, 40/10 mg, 80/5 mg and 80/10 mg strengths. The tablets will be packaged in peel-push aluminum blisters (10 tablets per card).

**EER Status:** Acceptable, 1-Oct-09

**Consults:** ONDQA Biopharmaceutics : Acceptable with a post-marketing commitment by the applicant to submit the new dissolution data along with the proposed new methodology and/or specifications to the Agency for review in one year from the day of issuance of the approval letter. Methods Validation – Revalidation by Agency was not requested. EA – FONSI by Raanan Bloom as per 11-Sep-09

## **II. Summary of Chemistry Assessments**

### **A. Description of the Drug Product(s) and Drug Substance(s)**

#### **Drug Substance:**

**Amlodipine besylate:** Amlodipine besylate is a white to almost white powder which is known to exist in 3 polymorphic forms – anhydrous, monohydrate and dihydrate. It was demonstrated that the current drug product contains only the anhydrous form and that no conversion of the different hydrates occurs under long term storage conditions.

Amlodipine besylate has one stereogenic center and is synthesized as a racemate. The CMC information for amlodipine besylate has been referenced to (b) (4) held by (b) (4). The DMF was reviewed by the CMC reviewer and found to be adequate to support this application. There is an existing USP monograph and the drug substance specification meets the compendial requirements. Additionally, the specification also includes appropriate controls for the particle size.

**Tesmisartan** is a white to slightly yellowish solid, known to exist in two polymorphic forms and is insoluble in water. The CMC information for telemisartan has been referenced to the currently approved NDA 20-850 for telemisartan tablets.

**Conclusion: Acceptable.**

**Drug product:** Twynista tablets are (b) (4) bilayer, oval, biconvex, immediate-release tablets, debossed on white layer with the company symbol and "A1", "A2", "A3" and "A4" for the 40/5 mg, 40/10 mg, 80/5 mg and 80/10 mg strengths, respectively. (b) (4)

(b) (4) The telmisartan layer in all strengths is dose proportional and is manufactured using same blend as used in the currently marketed Micardis and Micardis HCT tablets. (b) (4)

(b) (4) The tablets are manufactured using (b) (4)  
The quality of the drug product is assured through in-process controls and final drug product specification. The drug product specification include tests and acceptance criteria for appearance, identification (HPLC and TLC), dissolution, water content, resistance to crushing, degradation products (HPLC), microbial limits, uniformity of dosage forms by content uniformity and assay (HPLC). All analytical procedures used for the analysis are appropriately validated.

An expiration period of 24 months is being assigned to this product based on the submitted stability data when stored in the commercial packaging system at room temperature.

**Overall conclusion:** The application is recommended for approval from CMC perspective.

**Additional Items:** None

Ramesh Sood, Ph.D.  
Branch Chief/DPA1/Branch 1/ONDQA

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAMESH K SOOD  
10/14/2009

## MEMORANDUM

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

**DATE:** October 9, 2009

**FROM:** David J. Claffey, Ph.D., ONDQA

**SUBJECT:** **Final CMC recommendation for**  
NDA 22-401, Twynsta (telmisartan / amlodipine tablets)

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 it 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.

(B) 1 page of Draft labeling has been withheld immediately following this page as b  
(4) CCI



# ATTACHMENT 2

## FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

<b>Application:</b> NDA 72401-000	<b>Action Goal:</b>	
<b>Stamp Date:</b> 18-DEC-2008	<b>District Goal:</b>	19-AUG-2009
<b>Regulatory:</b> 18-OCT-2009		
<b>Applicant:</b> BOEHRINGER PHARMS 500 RIDGEBURY RD RIDGEBURY, CT 06877	<b>Brand Name:</b>	TELSARTAN/AMLODIPINE FIXED DOSE COM TB
	<b>Estab. Name:</b>	
	<b>Generic Name:</b>	TELSARTAN/AMLODIPINE FIXED DOSE COM TB
<b>Priority:</b> 4S	<b>Product Number, Dosage Form, Ingredient, Strengths</b>	
<b>Org. Code:</b> 110	001: TABLET, TELSARTAN, 40MG 001: TABLET, AMLODIPINE BESYLATE, EQ 5MG BASE 002: TABLET, TELSARTAN, 40MG 002: TABLET, AMLODIPINE BESYLATE, EQ 10MG BASE 003: TABLET, TELSARTAN, 80MG 003: TABLET, AMLODIPINE BESYLATE, EQ 5MG BASE 004: TABLET, TELSARTAN, 80MG 004: TABLET, AMLODIPINE BESYLATE, EQ 10MG BASE	

**Application Comment:**

<b>FDA Contacts:</b> D. HENRY	<b>Project Manager</b>	301-796-4227
K SRINIVASACHAR	<b>Team Leader</b>	301-796-1760

**Overall Recommendation:** ACCEPTABLE on 01-OCT-2009 by E. JOHNSON (HFD-320) 301-796-3334

## FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

**Establishment:** CFR: (b) (4)      FE: (b) (4)

**DMF No:**      **AADA:**

**Responsibilities:** (b) (4)  
(b) (4)

**Estab. Comment:**

**Profile:** (b) (4)      **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Submitted to OC	20-JAN-2009			RECEIVED	HENRYD
SUBMITTED TO DO	03-FEB-2009	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	09-FEB-2009	GMP Inspection			JOHNSONE
INSPECTION SCHEDULED	21-APR-2009		10-JUN-2009		IRIVERA
INSPECTION PERFORMED N/A	10-JUN-2009		10-JUN-2009		IMMAGERT
DO RECOMMENDATION	23-AUG-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	23-AUG-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 9613321 FEI: 3002806459  
BOEHRINGER INGELHEIM  
AVENIDA POMAREDA  
BARCELONA, , SPAIN

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE LABELER  
DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

**Estab. Comment:**

**Profile:** NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-MAR-2009				HENRYD
SUBMITTED TO DO	09-MAR-2009	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	09-MAR-2009	GMP Inspection			JOHNSONE
ASSIGNED INSPECTION TO IB	23-APR-2009	Product Specific			JOHNSONE
INSPECTION PERFORMED	16-JUL-2009		16-JUL-2009		AZZA.TALAAAT

**SUMMARY**

This was a Pre-Approval Inspection of Active Pharmaceutical Ingredients (APIs) manufacturer. The inspection was conducted at the request of DFI-International Operation HFC-134, HFD-325, (Attachment # 1) and FACTS assignment # 5111648. The inspection was completed in accordance with CP.7346.832, NDA Pre-Approval Inspections/ Investigations and CP.7356.002F, Active Pharmaceutical Ingredients. The Telmisartan API will be used in the manufacturing of Telmisartan /Amiodipine fixed dosage 40/5, 40/10, 80/5, 80/10 mg tablets NDA 22401/000. The applicant is: Boehringer Pharmaceuticals located at 1400 South Orange Ave. Orlando, FL 32806.

(b) (4)

This current inspection covered four systems; Facility / Equipment System, Quality System, Material System and the Laboratory System. The inspection revealed minor deficiencies that were observed and discussed with the firm's management as verbal observations.

At the conclusion of the inspection, on 7/16/09 the verbal comments were discussed with firm's managements. Management agreed to comments and correction promised.

INSPECTION PERFORMED 16-JUL-2009 16-JUL-2009 AZZA.TALAAAT

**SUMMARY**

This was a Pre-Approval Inspection of Active Pharmaceutical Ingredients (APIs) manufacturer. The inspection was conducted at the request of DFI-International Operation HFC-134, HFD-325, (Attachment # 1) and FACTS assignment # 5111648. The inspection was completed in accordance with CP.7346.832, NDA Pre-Approval Inspections/ Investigations and CP.7356.002F, Active Pharmaceutical Ingredients. The Telmisartan API will be used in the manufacturing of Telmisartan /Amiodipine fixed dosage 40/5, 40/10, 80/5, 80/10 mg tablets NDA 22401/000. The applicant is: Boehringer Pharmaceuticals located at 1400 South Orange Ave. Orlando, FL 32806.

(b) (4)

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System and the Laboratory System. The inspection revealed minor deficiencies that were observed and discussed with the firm's management as verbal observations.

At the conclusion of the inspection, on 7/16/09 the verbal comments were discussed with firm's managements. Management agreed to comments and correction promised.

DO RECOMMENDATION 31-AUG-2009 ACCEPTABLE JOHNSONE  
INSPECTION

OC RECOMMENDATION 31-AUG-2009 ACCEPTABLE JOHNSONE  
DISTRICT RECOMMENDATION

Establishment: CFN: 1119057 FEI: 1119057  
 BOEHRINGER INGELHEIM CHEMICALS INC  
 2820 NORMANDY DR  
 PETERSBURG, VA 238050058

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER  
 DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE PACKAGER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER

Estab. Comment:

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	03-MAR-2009				HENRYD
OC RECOMMENDATION	05-MAR-2009			ACCEPTABLE BASED ON PROFILE	KIEL

Establishment: CFN: 9610492 FEI: 3002906556  
 BOEHRINGER INGELHEIM PHARMA KG  
 D-55216 INGELHEIM AM RHEIN  
 INGELHEIM, GERMANY

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER  
 DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE PACKAGER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER  
 FINISHED DOSAGE LABELER  
 FINISHED DOSAGE MANUFACTURER  
 FINISHED DOSAGE PACKAGER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

Estab. Comment:

Profile: (b) (4) OAI Status: NONE  
 TABLETS, PROMPT RELEASE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	03-MAR-2009				HENRYD
SUBMITTED TO DO	09-MAR-2009	Product Specific			ADAMSS
DO RECOMMENDATION	09-MAR-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	09-MAR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	26-JAN-2009				HENRYD
SUBMITTED TO DO	03-FEB-2009	Product Specific			ADAMSS
DO RECOMMENDATION	09-FEB-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	10-FEB-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: (b) (4) (h) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Estab. Comment:

Profile: (h) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	26-JAN-2009				HENRYD
SUBMITTED TO DO	27-JAN-2009	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	05-FEB-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	24-MAR-2009		10-MAY-2009		IRIVERA
INSPECTION PERFORMED	09-APR-2009		09-APR-2009		VLADAMATUSOVSKY

(b) (4)

( ) ACCEPTABLE STOCKM  
DISTRICT RECOMMENDATION

Establishment: CFN: (b) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Estab. Comment:

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	26-JAN-2009				HENRYD
SUBMITTED TO DO	27-JAN-2009	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	05-FEB-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	24-MAR-2009		30-APR-2009		IRIVERA
INSPECTION PERFORMED	26-MAR-2009		26-MAR-2009		VLADA.MATUSOVSKY

(b) (4)

(b) (4) ACCEPTABLE JOHNSONE  
BASED ON FILE REVIEW

(b) (4) ACCEPTABLE JOHNSONE  
DISTRICT RECOMMENDATION

Establishment: CFN: (b) FEI: (b)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Estab. Comment:

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	26-JAN-2009				HENRYD
SUBMITTED TO DO	03-FEB-2009	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	05-FEB-2009	Product Specific			JOHNSONE
DO RECOMMENDATION	01-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	01-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

Establishment: CFN: (b) FEI: (b)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Estab. Comment: (b) (4) JPH

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<b>Comment</b>					
SUBMITTED TO OC	26-JAN-2009			Reason	HENRYD
SUBMITTED TO DO	03-FEB-2009	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	10-FEB-2009	GMP Inspection			JOHNSONE
INSPECTION SCHEDULED	05-APR-2009		06-MAY-2009		IRIVERA
DO RECOMMENDATION	23-AUG-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	27-AUG-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

Establishment: CFN: (b) FEI: (b)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

(b) (4)

Estab. Comment: Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<b>Comment</b>					
SUBMITTED TO OC	26-JAN-2009			Reason	HENRYD
SUBMITTED TO DO	27-JAN-2009	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	26-FEB-2009	GMP Inspection			JOHNSONE
INSPECTION SCHEDULED	21-APR-2009		27-MAY-2009		IRIVERA
INSPECTION PERFORMED	27-MAY-2009		27-MAY-2009		MHAGGERT
Refer to the Endorsement Text section of this report.					
DO RECOMMENDATION	02-JUN-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	02-JUN-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

Establishment: CFN: (b) FEI: (b)

(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

(b) (4)

Estab. Comment: Profile: (b) (4) OAI Status: NONE  
(b) (4) NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<b>Comment</b>					
SUBMITTED TO OC	26-JAN-2009			Reason	HENRYD
OC RECOMMENDATION	26-JAN-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	26-JAN-2009				HENRYD
OC RECOMMENDATION	26-JAN-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22401	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB

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

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/s/

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DAVID J CLAFFEY  
10/14/2009

RAMESH K SOOD  
10/14/2009



# **NDA 22-401**

**Twynista  
Telmisartan/Amlodipine Tablets**

**Boehringer Ingelheim**

**David J. Claffey, PhD  
ONDQA**



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# Chemistry Review Data Sheet

1. NDA 22-401
2. REVIEW #:1
3. REVIEW DATE: 20 AUG 2009
4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

N-001

BL (updated carton labeling)

BC (provided drug product samples)

BC (response to CMC IR)

Amendment (updated drug product specification)

Document Date

18 DEC 2008

10 JUL 2009

15 JUL 2009

24 JUL 2009

14 AUG 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.  
Address: 900 Ridgbury Road, Ridgefield, CT 06877  
Representative: Monika Richter



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Telephone:

203 791 6540

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Twynsta
- b) Non-Proprietary Name (USAN): telmisartan / amlodipine besylate
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 2
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: treatment of hypertension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

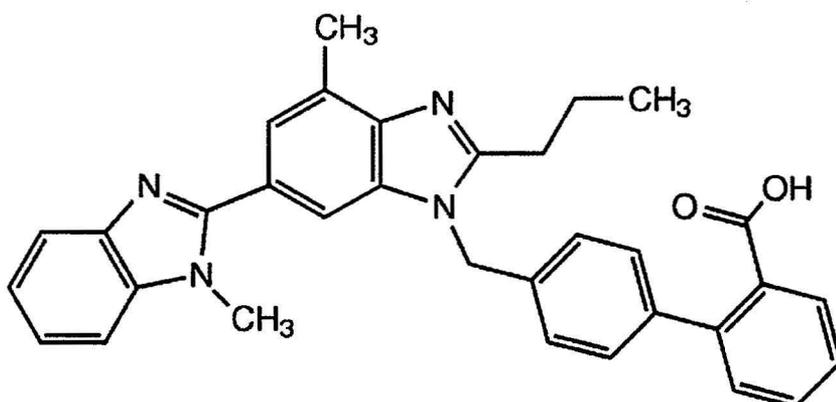
SPOTS product – Form Completed

Not a SPOTS product

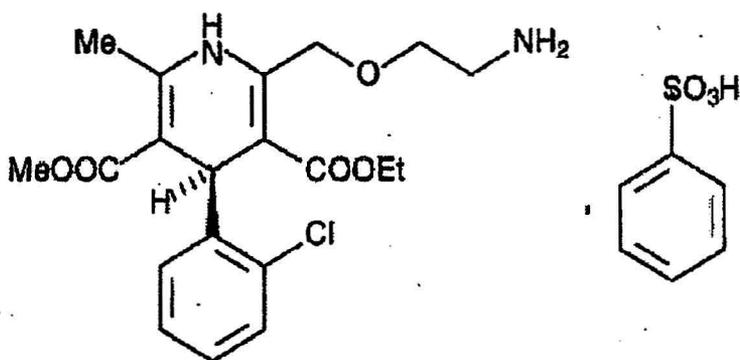
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Chemistry Review Data Sheet

## Telmisartan:



## Amlodipine Besylate:



and enantiomer

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) [REDACTED]	II	(b) (4)	Amlodipine besylate	1	Adequate	24 AUG 2009	
(b) [REDACTED]		(b) (4) g	(b) (4)	4			
(b) [REDACTED]		(b) (4)	(b) (4)	4			



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-850	Micardis (telmisartan tablets)
NDA	19-787	Norvasc (amlodipine besylate) tablets

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	pending		
Pharm/Tox	'approvable'	26 MAR 2009	Gowra Jagadeesh, PhD
Biopharm	Acceptable	7 MAY 2009	Islam R. Younis, PhD
EA	pending		Raanan Bloom, PhD
Biopharmaceutics	pending		Tien Mien Chen, PhD

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:

# The Chemistry Review for NDA 22-401

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Recommend that this application be approved from a CMC perspective on 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).

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

This application proposes the marketing of (b) (4) bilayer immediate-release tablets containing telmisartan and amlodipine in four different strength combinations:

- Telmisartan 40 mg and amlodipine 5 mg tablet (40/5 mg)
- Telmisartan 40 mg and amlodipine 10 mg tablet (40/10 mg)
- Telmisartan 80 mg and amlodipine 5 mg tablet (80/5 mg)
- Telmisartan 80 mg and amlodipine 10 mg tablet (80/10 mg)

(b) (4)

Both drug substances are labeled in terms of their **non-salt equivalents** – telmisartan being present as the sodium salt and amlodipine as the besylate salt. The tablets are oval, biconvex in shape - (b) (4)

The tablets are packaged in peel-push aluminum blisters (10 tablets per card). Tablet weights are 680 mg for the 80/5 mg and 80/10 mg tablets and 440 mg for the 40/5 mg and 40/10 mg strengths.

**Telmisartan layer:** (b) (4)

## Executive Summary Section

(b) (4)

**Tablets:**

(b) (4)

The tablets are manufactured, packaged, labeled and tested by (b) (4). Packaging and labeling also takes place at Boehringer Ingelheim Roxane, Inc., Columbus, OH. Stability data was provided on three pilot-scale batches (three lots of each strength in the proposed packaging configurations) up to 18 months at  $25^{\circ}\text{C}\pm 2^{\circ}\text{C}/60\%\pm 5\%\text{RH}$  and six months at  $40^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$ . No significant changes in product quality was observed. Stress, photostability and in-use stability studies were also carried out. Developmental studies demonstrated that the tablets are sensitive to light and humidity. Exposure of unpackaged tablets to humidities above 50% can cause them to deliquesce. The same drug product formulation was used throughout the proposed studies. (b) (4)

Stability data support the proposed 24-month drug product expiry period.

**DRUG SUBSTANCES:**

**Amlodipine besylate** is a white or almost white powder which is known to exist in 3 morphic forms – anhydrous, monohydrate and dihydrate. It was demonstrated that the drug product contains only the anhydrous form and that no conversion of the different hydrates occurs under long term storage conditions. Amlodipine besylate has one stereogenic center and is synthesized as a racemate. It is considered to be a BCS Class 1 drug substance. The supplier of this drug substance is (b) (4) and CMC information is provided in DMF (b) (4). This was found to be adequate on 24 AUG 2009 by this reviewer. The drug substance specification meets compendial



Executive Summary Section

requirements. It is known to be sensitive to light. In addition it has controls over the particle size distribution.

**Tesmisartan** is described in this application as the other drug substance. It is described as a white to slightly yellowish solid, known to exist in two polymorphic forms and insoluble in water. It is converted to the sodium salt (referred to by the applicant as (b) (4) by **Boehringer Ingelheim**, Germany then shipped to (b) (4) India for tablet manufacture. The sodium salt and (b) (4) are known to be sensitive to water. Adequate controls over storage and stability of the sodium salt are in place.

**B. Description of How the Drug Product is Intended to be Used**

The usual starting dose for initial therapy is 40/5 mg once daily. Patients requiring larger blood pressure reductions may be started on 80/5 mg once daily. Doses can then be titrated upwards as needed to a maximum dose of 80/10 mg once-daily.

**C. Basis for Approvability or Not-Approval Recommendation**

All issues raised in the 25 JUN 2009 information request have been adequately resolved. (b) (4) for amlodipine besylate was found to be adequate. An approval recommendation can be made on receipt of an 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).

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**

(C) 114 pages withheld immediately following this page as b(4) TS

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22401	ORIG 1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB
NDA 22401	ORIG 1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB
NDA 22401	ORIG 1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB
NDA 22401	ORIG 1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB
NDA 22401	ORIG 1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB

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/s/

DAVID J CLAFFEY  
09/01/2009

RAMESH K SOOD  
09/02/2009

## Initial Quality Assessment Branch I

<b>OND Division:</b>	Division of Cardiovascular and Renal Products
<b>NDA:</b>	22-401
<b>Applicant:</b>	Boehringer Ingelheim
<b>Letter Date:</b>	18 Dec 2008
<b>Status Date:</b>	18 Dec 2008
<b>PDUFA Date:</b>	18 Oct 2009
<b>Tradename:</b>	Twynsta
<b>Established Name:</b>	Telmisartan and Amlodipine
<b>Dosage Form:</b>	Tablets, 40 mg/5 mg, 40 mg/10 mg, 80 mg/5 mg, and 80 mg/10 mg
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	Hypertension
<b>Assessed by:</b>	Kasturi Srinivasachar
<b>ONDQA Fileability:</b>	Yes

### Summary

This electronic NDA, in CTD format, is for a fixed dose combination product of telmisartan and amlodipine besylate. Telmisartan is an angiotensin receptor antagonist marketed by Boehringer under the tradename Micardis (NDA 20-850) and amlodipine besylate is a well-known calcium channel blocker marketed by Pfizer under the tradename Norvasc (NDA 19-787). Clinical trials, under IND 71,882, were conducted using commercially available single entity drug products, Micardis and Norvasc, and later bioequivalence studies to the fixed dose combination drug product were carried out for the highest and lowest strengths. Biowaivers have been sought for the two intermediate strengths.

A multidisciplinary pre-NDA meeting was requested by Boehringer and scheduled for June 10, 2008. Based on the meeting package submitted, preliminary responses were provided by the division and since there was agreement on most questions, Boehringer cancelled the meeting and a written agreement to some open issues was sent to the firm on June 13, 2008. Boehringer had only minor CMC questions regarding NDA format, executed batch records, cross referencing etc. They proposed to submit draft container labels for only one strength in the original NDA and provide the labels for the remaining strengths in an amendment after obtaining Agency feedback and this was accepted.

### Drug Substance

Telmisartan is a white to slightly yellow crystalline, achiral synthetic substance. It exists in two morphic forms, A and B with quite different crystal shape and melting points. The manufacturing process may yield a mixture of both forms or pure form A which is thermodynamically stable. Telmisartan belongs to BCS class 2. All CMC information concerning this drug substance has been referred to NDA 20-850.

Amlodipine besylate is a white or almost white powder which is known to exist in 3 morphic forms – anhydrous, monohydrate and dihydrate. It is claimed that the drug product contains only the anhydrous form and that no conversion of the different hydrates occurs under long term

storage conditions. Amlodipine besylate has one stereogenic center and is synthesized as a racemate. It is considered to be a BCS class 1 drug substance. The supplier of this drug substance is (b) (4) and CMC information is provided in (b) (4). There is an USP monograph for amlodipine besylate. (b) (4) has a history of prior reviews and the latest dated Mar. 29, 2007 concludes that the application is adequate. A few amendments have been submitted since then.

**Drug Product**

4 strengths of the combination drug product have been developed as bilayer, (b) (4) immediate release tablets. (b) (4)

(b). The white layer has a debossed code to differentiate the different strengths. (b) (4)

(b) (4) The drug product is packaged in (b) (4) aluminium blister packs.

(b) (4)

Standard specifications for solid oral dosage forms have been proposed. Degradation products of telmisartan and amlodipine are determined using two different RP-HPLC methods with UV detection. For dissolution testing, different media have been chosen for telmisartan (phosphate buffer, pH 7.5, 900 mL) and amlodipine (0.01 N HCl, 500 mL) while retaining the same paddle speed of 75 rpm. Testing for microbial limits will be performed on the first 5 commercial batches and if the results meet the acceptance criteria, at least one batch per year will be tested at release depending on production rate. Stability data have been provided on 3 pilot scale batches for each strength and each packaging configuration. Up to 12 months long term and 6 months accelerated data are available and based on these as well as a statistical evaluation of assay and water content attributes, a shelf life of 24 months is proposed. Stress, photostability and in-use stability studies have also been performed.

## Critical Review Issues

### Drug substance

- Amendments to DMF (b) (4) submitted after the last documented review should be evaluated.
- Are the proposed particle size distribution acceptance criteria for amlodipine besylate adequately justified to assure good content uniformity of the layered tablets?
- (b) (4) drug substance is not used in product manufacturing; rather, (b) (4) is supplied by Boehringer to the product manufacturer, (b) (4) Is it necessary to include the drug substance manufacturing facility in EES?

### Drug Product

- What acceptance testing is performed on telmisartan (b) (4) by the drug product manufacturer? Has a hold time been defined for this material and is this supported by data?
- How is blend uniformity of the amlodipine final blend assured?
- Is a NMT (b) (4) limit for (b) (4) in the finished product specification justified? It should be noted that Micardis tablets are moisture sensitive and become soft when exposed to high humidity. (b) (4) could some migration take place in the presence of water?
- The Applicant claims that amlodipine exists in the drug product only as the anhydrate even though two hydrates of amlodipine besylate are known. Is it possible to have partial conversion to the hydrates upon storage? Will this have any impact on product performance?
- The biopharmaceutics group in ONDQA should review the data in support of biowaivers for the two intermediate strengths and may also be informally consulted about the acceptability of the regulatory dissolution methods and acceptance criteria.
- Is skip-lot testing for microbial limits acceptable for batch release?

### Labeling

- The product description, "multilayered tablets", in the 'How Supplied' section of the package insert should be revised to (b) (4)
- The molecular weights of the drug substances should be included in the 'Description' section of the Package Insert.

### Comments and Recommendations

The application is fileable. Manufacturing, testing and packaging facilities have been entered into EES and the reviewer should verify the accuracy and completeness of the entries. A single CMC reviewer is recommended for this application.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead  
Ramesh Sood, Ph.D.  
Branch Chief

Feb. 6, 2009  
Date  
Feb. 6, 2009  
Date

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/s/

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Kasturi Srinivasachar  
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