CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-401

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

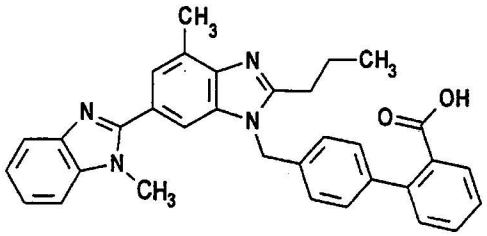
NDA NUMBER:	22,401
DATE RECEIVED BY CENTER:	December 18, 2008
DRUG PRODUCT:	TWYNSTA® Tablets
DRUG SUBSTANCE:	Telmisartan and Amlodipine
INTENDED CLINICAL POPULATION:	Hypertensive
SPONSOR:	Boehringer Ingelheim Pharmaceuticals, Inc.
REVIEW DIVISION:	Division of Cardiovascular and Renal Products
PHARM/TOX REVIEWER:	G. Jagadeesh, Ph.D.
PHARM/TOX SUPERVISOR:	Charles Resnick, Ph.D.
DIVISION DIRECTOR:	Norman Stockbridge, M.D., Ph.D.
PROJECT MANAGER:	Quynh M Nguyen

Date of review submission to Division File System (DFS): March 26, 2009

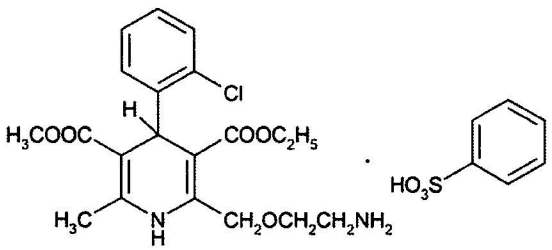
NDA number: 22,401
Date of Submission: 12-18-08
Center Receipt Date: 12-18-08
Reviewer Receipt Date: 12-26-2008
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc., USA
Manufacturer of Drug Substance: Telmisartan is from Boehringer Ingelheim International GmbH., Germany. Amlodipine besylate is from (b) (4)
Manufacturer of Drug Product: (b) (4) .
Reviewer: G. Jagadeesh, Ph.D.
Division: Division of Cardiovascular and Renal products
Review completion date: March 25, 2009

Drug Product: TWYNSTA® Tablets
Drug Substances

Generic name: **Telmisartan**
Code names: BIBR0277SE, BIBR 277 SE
Chemical name: 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid.
CAS registry number: 144701-48-4
Molecular formula/molecular weight: $C_{33}H_{30}N_4O_2$ / 514.63



Generic name: **Amlodipine Besylate**
Code name: LBT873-DMA.002
Chemical name: (*RS*)-2-[(2'-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl ester, 5-methyl ester, benzene sulfonate.
CAS registry number: 1114790-99-6 (besylate salt form), 88150-42-9 (free base form)
Molecular formula/molecular weight: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_5SO_3H$ / 567.06 (besylate)



Related Aplications: Boehringer Ingelheim Pharmaceuticals NDA 20,850 for Telmisartan (Micardis®) was approved for the treatment of hypertension in 1998. Pfizer's NDA 19,787 for racemic amlodipine besylate (Norvasc®) was approved for the treatment of hypertension, chronic stable angina and vasospastic angina in 1992.

Drug Class: Telmisartan: Angiotensin II receptor class 1 (AT_1 receptor) antagonist
Amlodipine: Dihydropyridine calcium channel blocker
Intended Clinical Population: Hypertensive subjects
Clinical Formulation: Immediate release tablets in four strengths: 40/5 mg, 40/10 mg, 80/5 mg and 80/10 mg (Telmisartan / Amlodipine). Excipients are shown in the following table.

COMPOSITION OF TELMISARTAN AND AMLODIPINE TABLET
(mg/dosage unit)

Ingredients	Tablet Strength [mg per tablet]				Function	Reference to standard
	40/5	40/10	80/5	80/10		
Telmisartan layer						
Telmisartan	40.000	40.000	80.000	80.000	Drug substance	Company Standard
Sodium hydroxide	(b) (4)	(b)	(b)	(b)	(b) (4) (b)	NF
Povidone (b)		(b)	(b)	(b)	(b) (4) (b)	USP
Meglumine		(b)	(b)	(b)	(b) (4) (b)	USP
(b) (4)		*	*	*	(b) (4)	USP
Sorbitol		(b) (4)			(b) (4)	NF
Magnesium stearate		(b)			(b) (4)	NF
						(b) (4)
Amlodipine besylate	(1)6.935	(2)13.870	(1)6.935	(2)13.870	Drug substance	USP
Microcrystalline cellulose	(b) (4)				(b) (4)	NF
Pregelatinized starch					(b) (4)	NF
Corn starch					(b) (4)	NF
Colloidal silicon dioxide					(b) (4)	NF
(b) (4)	(b) (4)				(b) (b) (4)	Company Standard
Magnesium stearate	(b) (4)				(b) (4)	NF
						(b) (4)
Total weight of layered tablet	440.000	440.000	680.000	680.000		

(b) (4)

Route of Administration: Oral
Proposed Dosage Regimen: One tablet daily.

EXECUTIVE SUMMARY

I. Background

Available evidence suggests that the majority of hypertensive individuals will require two or more antihypertensive drugs in order to achieve adequate control of blood pressure. Treatment with a single antihypertensive agent is often insufficient to control hypertension, as monotherapy inhibits only one of several pathophysiological mechanisms of this multifactorial disease.

Boehringer Ingelheim Pharmaceuticals has submitted a 505(b)(2) application for a fixed-dose combination of telmisartan and amlodipine besylate (Twynsta®) for the treatment of essential hypertension. Telmisartan is a non-peptidic, orally effective, specific antagonist of angiotensin II, active at the AT-1 receptor. Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group. It inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle, which results in peripheral arterial vasodilatation, reduction in peripheral vascular resistance and reduction in blood pressure. Both drugs have been extensively studied and are approved and widely used as monotherapies for the treatment of hypertension. Since these two drugs have different and complimentary modes of action, their combination should provide an additive or synergistic antihypertensive effect when compared to single drug treatment.

II. Recommendations

A. **Recommendation on Approvability:** Approvable

B. **Recommendations for Additional Nonclinical Studies:** None

C. **Recommendations for Labeling:** None

III. Summary of Nonclinical Findings

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).

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/s/

Gowra Jagadeesh
3/26/2009 11:01:43 AM
PHARMACOLOGIST

Charles Resnick
3/26/2009 02:15:56 PM
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