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RESEARCH**

APPLICATION NUMBER:

206302Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 206302
Supporting document/s: EDR
Applicant's letter date: 02/21/2014
CDER stamp date: 02/24/2014
Product: Nebivolol/valsartan
Indication: Hypertension
Applicant: Forest Laboratories, Inc.
Review Division: Cardiorenal Products
Reviewer: Philip Gatti, Ph.D.
Supervisor/Team Leader: Thomas Papoian, Ph.D., D.A.B.T.
Division Director: Norman Stockbridge, M.D., Ph.D.
Project Manager: Michael Monteleone

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1 Executive Summary

1.1 Introduction (and Clinical Rationale)

This is an application for a combination product that combines the beta-1 selective adrenoreceptor blocking drug, nebivolol with the angiotensin receptor blocker, valsartan. There are clinical studies that demonstrate partially additive anti-hypertensive effects when nebivolol was added to the regimen of patients who had not reached adequate BP control on Angiotensin Receptor Blocker monotherapy.

1.2 Brief Discussion of Nonclinical Findings

There are no new pharmacology or toxicology studies submitted to support this 505 b(2) application.

1.3 Recommendations

1.3.1 Approvability

This application is approvable from the pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

None

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

Generic Name

Nebivolol/valsartan

Code Name

N/A

Chemical Name

Nebivolol is (\pm) -[2R*[R*[R*(S*)]]]- α,α' -[iminobis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride

Valsartan is N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)-(1,1'-biphenyl)-4-yl] methyl]-(L)-valine OR N-(p-(O-1H-Tetrazol-5-ylphenyl)benzyl)-N-valeryl-(L)-valine OR N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-(L)-valine

Molecular Formula/Molecular Weight
Nebivolol- $C_{22}H_{25}F_2NO_4$. HCl; 441.90 g/mol
Valsartan- $C_{24}H_{29}N_5O_3$; 435.52 g/mol

Structure or Biochemical Description

Nebivolol

Figure 3.2.S.1.2.1-1. (SRRR)- or *d*-Nebivolol

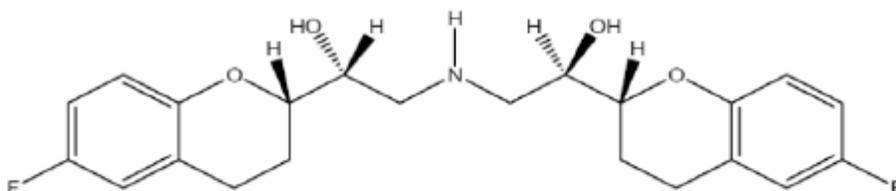
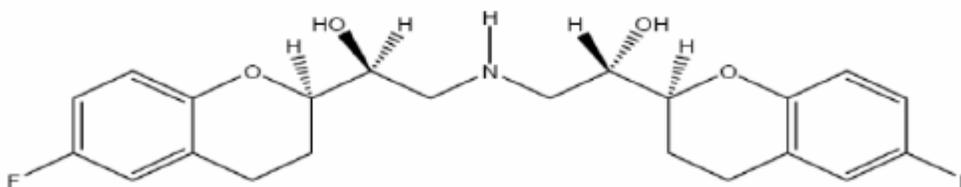
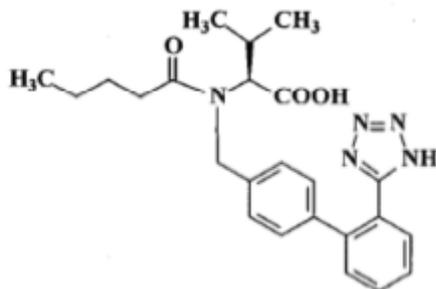


Figure 3.2.S.1.2.1-2. (RSSS)- or *l*-Nebivolol



Valsartan



Pharmacologic Class

Nebivolol is a beta-1 selective beta-adrenoreceptor antagonist

Valsartan is an angiotensin receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 21-742 Nebivolol

NDA 21-283 Valsartan

2.3 Drug Formulation

Nebivolol/Valsartan tablets, 5/80 mg

Table 3.2.P.1.2-1. Components and Quantitative Composition of Nebivolol/Valsartan Tablets, 5/80 mg

Component	Function	Quality Standard	Unit Dose Composition	
			(% w/w)	(mg/tablet)
			(b) (4)	(b) (4)
Nebivolol HCl	Drug substance	In-house ^a	(b) (4)	5.45 ^b
Lactose monohydrate, NF	(b) (4)	USP/NF	(b) (4)	(b) (4)
Microcrystalline cellulose, NF	(b) (4)	USP/NF	(b) (4)	(b) (4)
Copovidone, NF	(b) (4)	USP/NF	(b) (4)	(b) (4)
Croscarmellose sodium, NF	(b) (4)	USP/NF	(b) (4)	(b) (4)
Colloidal silicon dioxide, NF	(b) (4)	USP/NF	(b) (4)	(b) (4)
Magnesium stearate, NF	(b) (4)	USP/NF	(b) (4)	(b) (4)
Talc, USP	(b) (4)	USP/NF	(b) (4)	(b) (4)
Ferric oxide, NF	(b) (4)	USP/NF	(b) (4)	(b) (4)

2.4 Comments on Novel Excipients

No novel excipients

2.5 Comments on Impurities/Degradants of Concern

No impurities/degradants of concern

2.6 Proposed Clinical Population and Dosing Regimen

For efficacy, safety and tolerability: Patients with stage 1 or stage 2 essential hypertension; 1 week of screening followed by a single-blind placebo washout/run-in period of up to 6 weeks; followed by an 8-week double-blind treatment period; followed by a 1-week down-titration period. There are multiple smaller clinical studies to assess PK, bioavailability and bioequivalence.

2.7 Regulatory Background

Both nebivolol and valsartan have been approved by the FDA as agents used in the monotherapy of essential hypertension as noted above.

4 Pharmacology

No new non-clinical studies have been submitted

5 Pharmacokinetics/ADME/Toxicokinetics

No new non-clinical studies have been submitted.

6 General Toxicology

No new nonclinical studies have been submitted

7 Genetic Toxicology

No new nonclinical studies have been submitted

8 Carcinogenicity

No new nonclinical studies have been submitted

9 Reproductive and Developmental Toxicology

No new nonclinical studies have been submitted

11 Integrated Summary and Safety Evaluation

There were no nonclinical studies submitted for this 505b(2) application. The agents in this combination tablet (nebivolol/valsartan) have already undergone extensive nonclinical testing when they were reviewed previously as NDA's.

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/s/

PHILIP J GATTI
03/21/2014

THOMAS PAPOIAN
03/21/2014
Concur.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _____yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Philip J. Gatti, Ph.D.	04/03/2014
_____ Reviewing Pharmacologist	_____ Date
Thomas Papoian, Ph.D., D.A.B.T.	04/03/2014
_____ Team Leader/Supervisor	_____ Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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