CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209139Orig1s000

OTHER REVIEW(S)

RPM Overview – *AP Action*
NDA 209139
Prexxartan (valsartan) Oral Solution
4 mg/mL

Sponsor:	Carmel Biosciences, Inc.
Classification:	Standard
Letter Date:	December 30, 2016
User Fee Receipt Date:	December 30, 2016
Tentative Approval Date:	**October 30, 2017**
Resubmission Letter Date:	November 2, 2017
Resubmission Receipt Date:	November 2, 2017
User Fee Goal Date:	**January 2, 2018**

Background

Carmel Biosciences, Inc. received a Tentative Approval (TA) letter on October 30, 2017 for this 505(b)(2) NDA for Prexxartan (valsartan) Oral Solution, 4 mg/mL. The Tentative Approval letter was issued because of the unexpired patent/pediatric exclusivity on the 6294197 patent listed under Diovan, which had an expiry date of December 18, 2017. At the time, the unexpired patent/pediatric exclusivity was the only issue precluding a full approval. (Refer to my RPM Overview dated 10-30-17 regarding the TA action.)

The applicant resubmitted the application on November 2, 2017 and requested that the final approval be effective December 19, 2017.

Safety Update
As only 4 days had elapsed between issuance of the Tentative Approval letter and the applicant's resubmission, the Division determined that a safety update was not necessary.

Manufacturing Site Inspections
Per a 12-14-17 email from Dr. Wendy Wilson-Lee of OPQ, the facilities are in compliance.

Labeling
Three minor editorial corrections were made to the Content of Labeling on 12-14-17 to: (1) add the missing cross-reference "(4)" after "Known hypersensitivity" under the Contraindications listing in HIGHLIGHTS, (2) update the revision date from "10/2017" to "12/2017" and (3) to correct the typo "patents" to "patients" in Section 17 - Patient Counseling Information under Hyperkalemia. Per a 12-13-17 email, the applicant agreed with these edits.

505(b)(2) Clearance
Per a 11-14-17 email from Beth (Duvall) Goldstein, this application is "…cleared for approval on or after 12/19/17 from a 505(b)(2) perspective."

RPM Summary
An Approval (AP) Letter will be drafted for Dr. Stockbridge's signature.

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
12-19-17

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/s/

QUYNH M NGUYEN
12/19/2017

RPM Overview – *TA Action*
NDA 209139
Prexxartan (valsartan) Oral Solution
4 mg/mL

Sponsor:	Carmel Biosciences, Inc.
Classification:	Standard
Letter Date:	December 30, 2016
User Fee Receipt Date:	December 30, 2016
User Fee Goal Date:	October 30, 2017

Background

Carmel Biosciences, Inc. submitted this 505(b)(2) NDA for Prexxartan (valsartan) Oral Solution, 4 mg/mL. The proposed indications are the same as for the listed drug Novartis Pharmaceutical Corporation's Diovan Tablets (NDA 21-283) approved on July 18, 2001, i.e., for the treatment of hypertension, the treatment of heart failure (NYHA class II – IV), and to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

A Pre-IND Meeting was scheduled for December 5, 2013 to discuss the sponsor's development plans and intention to submit a 505(b)(2) NDA, but was cancelled at the sponsor's request because the FDA Preliminary Comments dated November 27, 2013 were sufficient.

Carmel Biosciences, Inc. submitted IND 119,968 on September 5, 2014.

An Agreed iPSP – Agreement Letter was issued on November 21, 2016.

No EOP2 meeting or Pre-NDA meeting was requested by the applicant.

In support of approval, the applicant is relying on the Agency's previous finding of safety and efficacy for the listed drug, Diovan Tablets, as well as on data from their two clinical studies (a comparative BA study and a food-effect study).

The applicant initially submitted a Paragraph I patent certification in their original NDA submission stating that "…there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs." However, as there were two unexpired patents for Diovan listed in the Orange Book at the time, the applicant later submitted on April 13, 2017 a Paragraph III patent certification stating that "Carmel Biosciences hereby commits to not market Valsartan Oral Solution, 4 mg/mL until the above referenced patent (6294197) has expired."

A small business waiver of the PDUFA application fee was granted on April 14, 2016.

Cross-Discipline Team Leader (CDTL) Review
In his review dated 10-29-17, Dr. Hariharan wrote the following:

> *Recommended Regulatory Action*
> Approval
>
> *Risk Benefit Assessment*
> For hypertension indication, the risk-benefit of Prexxartan when used as directed (twice-daily) in the proposed label is not expected to be different compared to Diovan.
>
> For heart failure and post-MI patients who cannot swallow a solid oral dosage form, there is a potential risk for hypotension due to higher Cmax with Prexxartan. However, this potential risk

is outweighed by the benefit of reducing the risk for cardiovascular morbidity and mortality events in these patients.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for other Postmarketing Requirements (PMR) and Commitments

- A deferred pediatric study under PREA in patients 2 to 5 years of age with hypertension using a revised formulation of Prexxartan containing lower propylene glycol content.
- A relative BA study in adults to compare the exposure to valsartan between the revised formulation of Prexxartan containing (b) (4) propylene glycol and the currently to-be-marketed formulation containing (b) (4) propylene glycol (to be conducted prior to the pediatric study).

Recommended Comments to Applicant
None

Dr. Stockbridge also signed the CDTL review in DARRTS on 10-30-17.

The following **primary reviews** were completed (see DAARTS for the complete reviews):

Discipline	Reviewer	Completion Dates
Quality Assessment	Mohan Sapru, Ph.D. (ATL)	10-13-17
Non-clinical	Gowra Jagadeesh, Ph.D.	4-5-17; 9-27-17
Clinical Pharmacology	Snehal Samant, Ph.D.	10-24-17
Clinical	Kimberly Smith, M.D.	7-31-17
Statistical	Ququan (Cherry) Liu, Ph.D.	2-23-17 (no review needed)
DMEPA	Ashleigh Lowery, Pharm.D., BCCCP, Sarah Thomas, Pharm.D.	3-23-17; 6-12-17; 7-11-17; 9-19-17
DPMH	Carrie Ceresa, Pharm D., MPH	6-6-17
OSIS	Shila Nkah	4-17-17
OPDP	Zarna Patel, Pharm.D.	8-15-17

Environmental Assessment
The sponsor requested a Categorical Exclusion for environmental assessment (EA); see Quality Assessment review.

Manufacturing Site Inspections
All currently listed manufacturing facilities are deemed acceptable by the Office of Process and Facilities; see Quality Assessment review.

Advisory Committee (AC) Meeting
Not applicable.

Debarment Certification
A debarment certification was submitted on 12-30-17.

Financial Disclosure
See Dr. Hariharan's 10-29-17 CDTL review.

Office of Scientific Investigations (OSI)
During the 45-day Filing Meeting on 2-22-17, it was agreed that clinical site inspections were not applicable.

Office of Study Integrity and Surveillance (OSIS)
OCP requested inspection of the clinical and bioanalytical site, [redacted] (b) (4) for the relative BA study CR-055-BE-2013. The Division of New Drug Bioequivalence Evaluation (DNDBE) within OSIS recommended accepting the data without an on-site inspection. See OSIS review dated 4-17-17.

Pediatrics
An Agreed iPSP – Agreement Letter was issued on 11-21-16 under the IND 119,968.

A PeRC meeting was held on 9-27-17 to discuss the applicant's proposal as follows:

Valsartan is approved for the treatment of hypertension in pediatric patients 6 to <17 years of age. Studies are not needed to establish safety and efficacy in this population. For the hypertension indication, the applicant requested a waiver in patients 0 to <2 years of age due to the renal maturation issues. For patients aged 2 to 5 years old with hypertension, the applicant plans to conduct two clinical studies (which will require the development of a revised formulation containing a lower quantity of propylene glycol). The applicant is requesting a deferral of these two pediatric studies since the drug product is ready for approval in adults. The two studies are as follows:

- A pharmacokinetic bridging study in adults to determine the exposure of valsartan with both the current and revised formulations of Valsartan Oral Solution prior to the conduct of studies in children. A revised formulation containing a lower quantity of propylene glycol is proposed for use in the clinical study for the 2 to 5 year old age group with hypertension.
- An efficacy and safety study of Valsartan Oral Solution in pediatric patients 2 to 5 years of age with hypertension.

The applicant requested full waivers for the heart failure and post-MI indications based on the rationale that studies are impossible or highly impractical.

The PeRC and Division agreed with the applicant's proposal. See Dr. Hariharan's 10-29-17 CDTL review and Dr. Smith's 7-31-17 Clinical review for additional information.

Labeling
Content of labeling was submitted in PLR format and includes a PPI. However, it was determined during the NDA review cycle that there will be no PPI for this product. Carton and container labeling was also submitted.

OPDP had no comments on the proposed labeling. See OPDP review dated 8-15-17.

DMEPA provided comments on the proposed labeling in reviews dated 6-12-17, 7-11-17, and 9-19-17.

Proprietary name review
A request for proprietary name review was submitted in the NDA. DMEPA found the proposed name "Prexxartan" acceptable on 3-23-17 (see DMEPA review). The proposed name had been found conditionally acceptable under the IND 119,968.

User Fee
Not applicable; a small business waiver was granted on 4-14-16.

505(b)(2) Clearance
Per a 10-11-17 email from Beth (Duvall) Goldstein, the application is "…cleared for a TA action at best from a 505(b)(2) perspective. Note that because of the unexpired patent/peds exclusivity on the '197 patent listed under Diovan, this application cannot be approved any earlier than 12/18/17 – hence the TA (at best) this review cycle."

RPM Summary
A Tentative Approval (TA) Letter will be drafted for Dr. Stockbridge's signature.

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
10-30-17

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/s/

QUYNH M NGUYEN
10/30/2017

MEMORANDUM

REVIEW OF LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 19, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209139
Product Name and Strength:	Prexxartan (valsartan) oral solution, 4 mg/mL
Applicant/Sponsor Name:	Carmel Biosciences
Submission Date:	August 31, 2017
OSE RCM #:	2017-106-2
DMEPA Primary Reviewer:	Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the newly submitted carton labeling for Prexxartan 120 mL bottle (Appendix A) to determine if it is acceptable from a medication error perspective. We previously reviewed container labels for the 30 mL unit dose cup and 120 mL and 473 mL bottles .[a,b] The applicant confirmed that they are not packaging the 20 mL unit dose cup or 473 mL bottle in a carton.

2 CONCLUSION

We performed a risk assessment of the proposed Prexxartan carton labeling to identify deficiencies that may lead to medication errors. We also compared the carton labeling to the previously reviewed container labels. All of our applicable previous recommendations are reflected in the carton labeling. After reviewing the carton labeling, we have additional recommendations in Section 3 below.

[a] Lowery A. Label and Labeling Review for Prexxartan (NDA 209139). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Jun 12. RCM No.: 2017-106.
[b] Lowery A. Label and Labeling Memo for Prexxartan (NDA 209139). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Jul 11. RCM No.: 2017-106-1.

3 RECOMMENDATIONS FOR CARMEL BIOSCIENCES

We recommend the following be implemented prior to approval of this NDA:

A. Remove the statement "(b) (4)" This may lead to confusion (b) (4) .

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/s/

ASHLEIGH V LOWERY
09/19/2017

CHI-MING TU
09/19/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

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

Date: August 15, 2017

To: Quynh M. Nguyen, PharmD, RAC
Regulatory Project Manager
Division of Cardiovascular Products (DCRP)

From: Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Prexxartan (valsartan) Oral Solution**
NDA: 209139
Draft product labeling

OPDP has reviewed the proposed Package Insert (PI) and Carton/Container Labeling submitted for consult on February 23, 2017, for Prexxartan (valsartan) Oral Solution. OPDP's review of the PI is based on the attached copy of the proposed labeling emailed to us on August 8, 2017 and we have no comments at this time. We note that the consult also requested a review of a Patient Package Insert (PPI), however, it was determined that there will be no PPI for this product.

OPDP has also reviewed the revised container labeling submitted by the sponsor on August 4, 2017 (EDR link for the submission: \\CDSESUB1\evsprod\NDA209139\0012). We have no comments on the proposed container labeling at this time.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
08/15/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 11, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209139
Product Name and Strength:	Prexxartan (valsartan) oral solution, 4 mg/mL
Applicant/Sponsor Name:	Carmel Biosciences
Submission Date:	June 30, 2017
OSE RCM #:	2017-106-1
DMEPA Primary Reviewer:	Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels for Prexxartan (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We compared the labels submitted on June 30, 2017 to those previously submitted on May 22, 2017 for our previous review. All of our recommendations were implemented. After reviewing the revised labels, we have additional recommendations in Section 3 below.

3 RECOMMENDATIONS FOR CARMEL BIOSCIENCES

We recommend the following be implemented prior to approval of this NDA:

A. Consider removing (b) (4) so that the strength of "80 mg/20 mL" can be more prominent.

[a] Lowery A. Label and Labeling Review for Prexxartan (NDA 209139). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Jun 12. RCM No.: 2017-106.

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/s/

ASHLEIGH V LOWERY
07/11/2017

CHI-MING TU
07/11/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 12, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209139
Product Name and Strength:	Prexxartan (valsartan) oral solution, 4 mg/mL
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Carmel Biosciences
Submission Date:	March 15, 2017 and May 5, 2017
OSE RCM #:	2017-106
DMEPA Primary Reviewer:	Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the proposed Valsartan oral solution container labels and prescribing information submitted on December 30, 2016 and March 15, 2017 for risk of medication error.

The NDA is a 505(b)(2) application referencing Diovan (NDA 021283).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Valsartan oral solution container labels and PI to identify deficiencies that may lead to medication errors and other areas for improvement.

Prescribing Information (PI)

We note that the dosage and titration instructions can be improved for clarity. NDC numbers are also not listed in the PI. We provide recommendations in Section 4.1.

Container Labels

We identified that NDC numbers are denoted by placeholders and request that the numbers be submitted for reviews. We also found that the strength presentations can be improved. We provide recommendations in Section 4.2 to increase clarity and promote safe use.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed Valsartan oral solution container labels and PI that can be improved to increase clarity and add important information to promote the safe use of this product. We provide recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. See Appendix H for our recommendation for the proposed Prescribing Information.

4.2 RECOMMENDATIONS FOR CARMEL BIOSCIENCES

We recommend the following be implemented prior to approval of this NDA:

A. General
   1. The NDC numbers are currently denoted by a placeholder (XXXXX-XXXX-XX). Please submit the actual NDC numbers for our review.
   2. Add a space between the numerical strength and unit of measure on all labels (e.g., 4 mg/mL instead of 4mg/mL).
   3. Relocate the strength statement to immediately below the established name and dosage form. For example,

Prexxartan
(valsartan) Oral Solution
mg/## mL
(4 mg/mL)

B. Container Label – 120 mL and (b) (4) mL bottles
   1. Consider revising the presentation of the strength to 20 mg/5 mL (4 mg/mL). Providing the mg per 5 mL, in addition to 4 mg/mL, may help healthcare providers calculate higher doses (e.g., 80 mg, 160 mg, etc.) more efficiently and with less risk of error.

C. Container Label – 20 mL unit dose cup
   1. Revise the presentation of the strength to reflect the total contents of the unit dose cup: 80 mg/20 mL (4 mg/mL).
   2. Ensure that the lot number is clearly labeled. As presented, it is not clear which numbers are the lot number.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Valsartan oral solution that Carmel Biosciences submitted on May 5, 2017, and the listed drug (LD).

Table 2. Relevant Product Information for Valsartan oral solution and the Listed Drug

Product Name	**Valsartan oral solution**	**Diovan (NDA 021283)**
Initial Approval Date	N/A	July 18, 2001
Active Ingredient	Valsartan	Valsartan
Indication	For the treatment of hypertension For the treatment of heart failure (NYHA class II-IV) Reduction in cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction	For the treatment of hypertension For the treatment of heart failure (NYHA class II-IV) Reduction in cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction
Route of Administration	Oral	Oral
Dosage Form	Solution	Tablet
Strength	4 mg/mL	40 mg, 80 mg, 160 mg, and 320 mg
Dose and Frequency	Adult: 80 mg to 320 mg once daily Pediatric: (b) (4)	80 mg to 320 mg daily
How Supplied	Bottles of 120 mL and 473 mL Unit dose cups of 20 mL	Bottles of 30 tablets, 90 tablets, or 100 tablets; Unit dose blister packages
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°F (59°F to 86°F)	Store at 25°C (77°F); excursions permitted to 15°C to 30°F (59°F to 86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 3, 2017, we searched the L:drive and AIMS using the term, “valsartan,” to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On March 3, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing, Quarterly Action Agenda, Canada Safety Bulletin
Search Strategy and Terms	Match Exact Word or Phrase: valsartan

D.2 Results

We did not identify any newsletters with articles relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Valsartan oral solution labels and labeling submitted by Carmel Biosciences.

(b) (4)

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

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/s/

CHI-MING TU on behalf of ASHLEIGH V LOWERY
06/12/2017

CHI-MING TU
06/12/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: June 6, 2017 **Date consulted:** April 6, 2017

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Jane Liedtka, M.D., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Prexxartan (valsartan) 4 mg/mL oral solution

NDA: 209139

Applicant: Carmel Biosciences, Inc.

Subject: Pregnancy and Lactation Labeling Rule Review

Indication: for the treatment of hypertension; treatment of heart failure (NYHA class II-IV); and in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, to reduce cardiovascular mortality

Materials Reviewed:

- April 6, 2017, Maternal Health, DPMH consult, DARRTS Reference ID 4081220
- December 30, 2016 & May 5, 2017, New Drug Application, NDA 209139
- (b) (4)
-

Consult Question: **"**We would like DPMH to review the PLLR labeling changes to the content of labeling."

INTRODUCTION

The Division of Cardiovascular and Renal Drug Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of valsartan oral solution labeling.

REGULATORY HISTORY

On December 30, 2016, Carmel Biosciences submitted NDA 209139, a 505(b)(2) application for Prexxartan (valsartan) oral solution 4 mg/mL relying on the safety and efficacy of the reference listed drug (RLD) Diovan (valsartan) tablets (320 mg) NDA 21283 which was initially approved in July 18, 2001. The proposed indication for NDA 209139 is as follows:

- For the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions
- Treatment of heart failure (NYHA class II-IV); valsartan significantly reduced hospitalization for heart failure
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction

BACKGROUND

Drug Characteristics[1,2]

Valsartan is an angiotensin II receptor blocker with effects that block the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Valsartan has a molecular weight of 435.52 g/mol, protein-binding of 95%, bioavailability of 25%, and a half-life of six hours. Adverse reactions that have been seen in clinical trials and in post-marketing reports include: angioedema, cough, renal failure, hepatitis, hypotension, and hyperkalemia.

Cardiovascular Disease and Pregnancy[3,4,5]

Common minor abnormalities occur in the heart rhythm during pregnancy. Blood volume and the amount of blood the heart pumps per minute increases 30% to 50% during pregnancy. Cardiovascular Disease (CVD) complicates 1-4% of pregnancies, with congenital heart disease

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[1] (b) (4)

[2] Diovan (valsartan). FDA approved labeling 2/3/2017. Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021283. Accessed 16 May 2017.

[3] Pregnancy week by week. Mayo Clinic. http://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/pregnancy/art-20045977. Accessed 16 May 2017.

[4] (b) (4)

[5] Naderi, Sahar and Raymond, Russell. 2014, Pregnancy and Heart Disease. Cleveland Clinic Center for Continuing Education. https://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/pregnancy-and-heart-disease/. Accessed 16 May 2017.

being the most common preexisting condition and hypertension being the most common acquired condition. Women with heart failure of any etiology with an ejection (EF) <40% or NYHA class III-IV symptoms should be counseled to avoid pregnancy. Hypertrophic cardiomyopathy (HCM), which can cause heart failure, is associated with an increased maternal morbidity and mortality. Tachycardia and a decrease in systemic vascular resistance, which can occur during pregnancy, can exacerbate outflow tract obstruction in patients with HCM.

Current State of the Labeling

Current valsartan labeling for the RLD is in the PLR format but not the PLLR format and has a boxed warning for fetal toxicity for valsartan and all angiotensin II receptor blockers because drugs that act directly on the renin-angiotensin system can cause death or serious injury to the developing fetus. Serious neonatal adverse events that can occur include skull hypoplasia, anuria, hypotension, renal failure and death. These outcomes are usually associated with second and third trimester exposure. The labeling also notes that if pregnancy occurs during use, valsartan should be discontinued. The pregnancy and lactation labeling the RLD labeling contain the following language:

> **8.1 Pregnancy**
> **Pregnancy Category D**
> Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Diovan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.
>
> In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Diovan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Diovan for hypotension, oliguria, and hyperkalemia [see Use in Specific Populations (8.4)].
>
> **8.3 Nursing Mothers**
> It is not known whether Diovan is excreted in human milk. Diovan was excreted in the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because

of the potential for adverse reactions in nursing infants from Diovan, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer comment: DPMH notes that the animal reproduction data are located in subsection 13.2 of the RLD labeling and not in subsection 8.1. DPMH recommends placing the animal reproduction data into subsection 8.1 in the Prexxartan labeling per the Pregnancy and Lactation Labeling Rule.[6]

Valsartan and Pregnancy

Valsartan should not be used during pregnancy. (see *Current State of Labeling* section above) There are no controlled clinical trials with valsartan and pregnancy. Valsartan is an angiotensin II receptor antagonist. It has long been known that angiotensin II type receptor antagonists can cause serious adverse events during pregnancy such as oligohydramnios, skull hypoplasia, anuria, hypotension, renal failure, newborn renal dysfunction and death. These adverse effects are already described in current valsartan labeling. It is believed that the fetal renin angiotensin system becomes active during the second trimester of pregnancy. The fetal adverse events described above have been observed during the second and third trimesters of pregnancy.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[6] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[7] format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Nonclinical Experience[2]

In animal reproduction studies, no teratogenic effects were observed after administration of valsartan oral at doses up to 600 mg/kg/day in rats and 10 mg/kg/day in rabbits. However, in rats, significant decreases in fetal weight, pup birth weight, pup survival rate and delays in developmental milestones were observed in doses up to 600 mg/kg/day during organogenesis or late gestation and lactation. Fetotoxicity was observed in rabbits at doses 5 and 10 mg/kg/day.

[6] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[7] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

Review of Literature

Applicant's Review of Literature

The applicant performed a systematic review of published case reports and case series dealing with intrauterine exposure to renin-angiotensin system inhibitors-including AT1 receptor antagonists using Medline. The applicant identified 35 articles (with 68 cases) describing the prenatal exposure to AT1 receptor antagonists. The applicant reports that 87% of the fetal exposures to AT1 receptor antagonists during second and third trimester from the literature they reviewed displayed complications. Neonatal complications included prematurity, renal failure, oligohydramnios, death, arterial hypotension, intrauterine growth retardation, respiratory distress syndrome, pulmonary hypoplasia, hypocalvaria, limb defects, persistent patent ductus arteriosus, cerebral complications, stillbirth, neonatal death and renal damage. There is little information known about valsartan exposure during the first trimester. The applicant submitted 12 publications in support of their labeling recommendations. Those found relevant for the purposes of this review are described in detail in Tables 1 and 2 in Appendix B.[8,9,10,11]

DPMH's Review of Published Literature

DPMH conducted a search of published literature in PubMed using the following search terms, "valsartan" and "pregnancy", "valsartan" and "spontaneous abortion" and "valsartan" and "fetal malformations". In addition to the literature submitted by the applicant 16 case reports were reviewed by DPMH and described in Table 3 in Appendix B that include valsartan exposure during pregnancy.[12,13,14,15,16,17,18,19,20,21,22,23]

[8] Bullo, M, et al, 2012, Pregnancy Outcome Following Exposure to Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Antagonists: A Systematic Review, Hypertension, 60:444-450.
[9] Walfisch, A, 2011, Teratogenicity of angiotensin converting enzyme inhibitors or receptor blockers, Journal of Obstetrics and Gynaecology, 31(6):465-472.
[10] Moretti, M, et al, 2012, The Fetal Safety of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers, Obstetrics and Gynecology International, 2012:1-6.
[11] Diav-Citrin, O, 2011, Pregnancy outcome after in utero exposure to angiotensin converting enzyme inhibitors or angiotensin receptor blockers, Reproductive Toxicology, 31:540-545.
[12] Berkane, N, et al, 2004, Fetal Toxicity of Valsartan and Possible Reversible Adverse Side Effects, Birth Defects Research (Part A), 70:547-549.
[13] Bos-Thompson, M, et al, 2005, Fetal Toxic Effects of Angiotensin II Receptor Antagonists: Case Report and Follow-Up after Birth, Ann Pharmacother, 39:157-61.
[14] Briggs G, and M Nageotte, 2001, Fatal Fetal Outcome with the Combined Use of Valsartan and Atenolol, Ann Pharmacother, 35:859-61.
[15] Chung N, et al, 2001, Outcomes in women given valsortam early in pregnancy, The Lancet, 357, 1620-1621.
[16] Martinovic J, et al, 2001, Fetal toxic effects and angiotensin-II-receptor antagonists, The Lancet, 358, 241-242.
[17] Saar T, et al, 2016, Case Report Reversible Fetal Renal Impairment following Angiotensin Receptor Blocking Treatment during Third Trimester of Pregnancy: Case Report and Review of the Literature, Case Reports in Obstetrics and Gynecology, 2016, 1-3.
[18] Tsepkentzi E, et al, 2016, Neonatal acute kidney injury following Valsartan exposure in utero: report of two cases, Hippokratia, 20(1): 73-75.
[19] Schaefer C. Angiotension II-receptor antagonists: further evidence of fetotoxicity but not teratogenicity, Birth Defects Research (Part A) 67:591–594 (2003).
[20] Shimada C, et al, 2015, The Japanese Society of Hypertension, 38:308-313.
[21] Hunseler C, et al, 2011, Angiotensin II receptor blocker induced fetopathy, Klin Pediatr, 223:10-2014.
[22] Schindera C, et al, 2012, Journal of Neonatal Biology, 1:1-2.
[23] Vendemmia M, et al, 2005, Fetal and neonatal consequences of antenatal exposure to type 1 angiotensin receptor antagonists, The Journal of Maternal-Fetal and Neonatal Medicine, 18(2):137-140.

As currently described in labeling, valsartan exposure during pregnancy is known to cause oligohydramnios, hypoplasia, anuria, hypotension, renal failure, and death. In addition, multiple published case reports as described in Appendix B also demonstrate anhydramnios in humans.

Summary
Although teratogenic effects have not been observed in animal reproduction studies with valsartan, it is widely known that valsartan can cause adverse events in human pregnancy as discussed above. Current valsartan labeling notes that oligohydramnios, hypotension, hyperkalemia, oliguria, neonatal skull hypoplasia, anuria, renal failure and fetal or neonatal death can occur when angiotensin II receptor antagonists are used during the second or third trimester of pregnancy. In addition to what is already in valsartan labeling, DPMH also recommends that additional language to be added with regard to anhydramnios. See labeling recommendations below.

LACTATION

Nonclinical Experience
Valsartan is excreted in rat milk. No additional information is known.

Review of Literature
Applicant's Review of Literature
The applicant conducted a review of published literature and a review in the LactMed[24] database on valsartan exposure during lactation and noted that no information is available on the use of valsartan during breastfeeding.

DPMH's Review of Literature
DPMH conducted a review of published literature using PubMed on the use of valsartan and breastfeeding and no information was located.

In Medications and Mother's Milk,[25] Dr. Thomas Hale, a breastfeeding expert notes that there are no data on the use of valsartan and lactating women and ARBs are contraindicated in pregnancy and there are other medications more suitable for maternal medical conditions.

In addition, it is unknown whether valsartan is present in human milk and serious adverse events have been observed in pediatric patients under the age of six. In a pediatric study (n=90) in subjects 1-5 years, two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. A causal relationship to valsartan was not established. In a second study of 75 pediatric subjects there were no deaths however one case of marked liver transaminase elevations.[2] Therefore breastfeeding is not recommended.

[24] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[25] Hale, T. Medication's and Mothers Milk. Springer Publishing Company, 2017.

Summary
There are no human or animal data on the use of valsartan and lactation. In addition, due to serious adverse events that have been observed in pediatric patients under the age of six breastfeeding is not recommended.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience
In animal reproduction studies valsartan showed no adverse effects on fertility in rat studies at doses up to 200 mg/kg/day (6 times the maximum recommended human dose on a mg/m^2 basis). See pharmacology/toxicology review in DARRTS).

Review of Literature
There are no published literature on the use of valsartan and possible effects on fertility.

Summary
The applicant proposed adding section 8.3 Females and Males of Reproductive Potential to labeling to demonstrate that there was no impairment of fertility in animal studies in rats. Because there are no infertility issues in humans or animals, subsection 8.3 Females and Males of Reproduction Potential will be omitted from valsartan labeling.

CONCLUSIONS
The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of TRADENAME labeling were structured to be consistent with the PLLR, as follows:

- **Warnings and Precautions, Section 5.1**
  - A subsection describing embryo- and/or fetal risks as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4)).
- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," section."
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

LABELING RECOMMENDATIONS
DPMH revised sections 5.1, 8.1, 8.2 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant's proposed pregnancy and lactation labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------

- Lactation*:* Breastfeeding not recommended. (8.2)

FULL PRESCRIBING INFORMATION
Boxed Warning

Warning: Fetal Toxicity

See Full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue Prexxartan as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury to the developing fetus. (5.1)**

5 Warnings and Precautions

5.1 Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Prexxartan as soon as possible *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prexxartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to angiotensin receptor blockers use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Studies in rats and rabbits with valsartan showed fetotoxicity only at maternally toxic doses (*see Data).* Published reports include cases of anhydramnios and oligohydramnios in pregnant women treated with valsartan. When pregnancy is detected, discontinue Prexxartan as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum

hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions
Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia and skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus.

In patients taking Prexxartan during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to Prexxartan for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occur in neonates with a history of *in utero* exposure to Prexxartan, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and substituting for disordered renal function.

Data
Animal Data
No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200, and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. Calculations assume an oral dose of 320 mg/day and a 60-kg patient.

8.2 Lactation
There are no data on the presence of Prexxartan in human milk, the effects on the breastfed infant, or the effects on milk production. Valsartan is present in rat milk. Because of the potential for valsartan to affect postnatal renal development in nursing infants, advise a nursing woman not to breastfeed during treatment with Prexxartan.

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to notify their healthcare provider with a known or

suspected pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Lactation

Advise women not to breastfeed during treatment with Prexxartan *[see Use in Specific Populations (8.2)]*.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CARRIE M CERESA
06/06/2017

JANE E LIEDTKA
06/06/2017

LYNNE P YAO
06/06/2017

M E M O R A N D U M

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

DATE: 4/17/2017

TO: Division of Cardiovascular and Renal Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209139

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	AnaCipher Clinical Research Organisation	3rd and 4th Floor, Mirra Kamshetty Mall, Ramanthapur, R.R. District, Hyderabad, Telangana, India
Analytical	(b) (4)	

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/s/

SHILA S NKAH
04/17/2017