

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205003Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205003	NDA Supplement #: N/A	Efficacy Supplement Type: N/A
Proprietary Name: PRESTALIA Established/Proper Name: Perindopril arginine/Amlodipine besylate Dosage Form: tablet Strengths: 3.5 mg/2.5 mg, 7 mg/5 mg, 14 mg/10 mg		
Applicant: Symplmed Pharmaceuticals LLC		
Date of Receipt: 3-21-2014		
PDUFA Goal Date: 1-21-2014		Action Goal Date (if different):
RPM: Wayne Amchin		
Proposed Indication(s): Hypertension		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 19787, NORVASC (amlodipine besylate)	FDA's previous finding of safety and effectiveness <u>Labeling Sections:</u> <ul style="list-style-type: none"> • Warnings and Precautions (Section 5) • Adverse Reactions (Section 6) • Drug-Drug Interactions (Section 7) • Use in Specific Populations (Section 8) • Nonclinical Toxicology (Sections 8 and 13) • Overdosage (Section 10) • Clinical Pharmacology (Section 12)
Published Literature: Vincent J, Harris SI, Foulds G, Dogolo LC, Willavize S, Friedman HL. Br J Clin Pharmacol 2000;50:455-463	This publication was submitted by the applicant. The data contained in this publication were used to conduct a cross-study comparison for exposures to amlodipine between NORVASC and the to-be-marketed formulation of PRESTALIA.

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information from another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Clinical Pharmacology: The applicant submitted the published literature (Vincent et al, 2000) containing summary PK data for NORVASC. The applicant compared the mean exposure measures (peak concentration (C_{max}) and area under the curve (AUC)) of amlodipine between NORVASC (amlodipine besylate 10 mg) and Prestalia (perindopril

arginine/amlodipine besylate 14/10 mg) and concluded that the exposure measures were similar. The clinical pharmacology reviewer concurred with the applicant's conclusions after determining the arithmetic ratios for the exposure measures of amlodipine between NORVASC and Prestalia show that the exposures were similar.

Nonclinical:

The applicant conducted a 13-week, repeat-dose, oral toxicity study in rats comparing the toxicokinetics and toxicity of perindopril arginine and amlodipine besylate administered alone and in combination.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

NORVASC

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
NORVASC	19787	Y (356h)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

Amlodipine besylate is approved in the United States as NORVASC but is not currently approved in combination with any form of perindopril.

The amlodipine besylate component of PRESTALIA (perindopril arginine/amlodipine besylate) is equivalent to that in NORVASC (amlodipine besylate), in the monotherapy sense for the active moiety.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "**YES**" to (c) **and** there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "**NO**" **or** if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do **not** have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

U.S. Patent No. 4,879,303 (Pfizer) expired on March 25, 2007 and U.S. Patent No. 4,572,909 (Pfizer) expired on July 31, 2006. Both of these patents are for NORVASC.

U.S. Patent No. 4,508,729, expired on August 20, 2006 and U.S. Patent No. 5,162,362, expired on November 10, 2009. Both of these patents are for ACEON. The current applicant (Symplmed Pharmaceuticals LLC) became the owner of ACEON NDA 20184 on August 8, 2014.

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

WAYNE S AMCHIN
01/21/2015

LABEL AND LABELING MEMO

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 : December 22, 2014
Requesting Office or Division: Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number: NDA 205003
Product Name and Strength: Prestalia (perindopril arginine and amlodipine) Tablets,
3.5 mg/2.5 mg, 7 mg/5 mg, 14 mg/10 mg
Product Type: Multi-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Symplmed Pharmaceuticals, Inc.
Submission Date: December 19, 2014
OSE RCM #: 2014-652-1
DMEPA Primary Reviewer: Janine Stewart, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 INTRODUCTION

This memorandum evaluates the revised container labels for Prestalia (perindopril arginine and amlodipine) Tablets, NDA 205003, submitted on December 19, 2014 (Appendix A). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2014-652 dated July 16, 2014¹.

2 MATERIAL REVIEWED

DMEPA reviewed the container labels submitted on December 19, 2014. We compared the revised labels against the recommendations contained in OSE Review # 2014-652 dated July 16, 2014¹.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cherye Milburn, at 301-796-2084.

¹ Stewart J. Label and Labeling Review for Prestalia (NDA 205003). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 JUL 16. 28 p. OSE RCM No.: 2014-652.

Appendix A:

(b) (4)



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/s/

JANINE A STEWART
12/22/2014

CHI-MING TU
12/23/2014

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

Memorandum

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

Date: December 12, 2014

To: Wayne Amchin
Regulatory Project Manager
Division of Cardiovascular and Renal Products

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

Subject: **Prestalia** (perindopril argenine and amlodipine) tablets for oral use
NDA 205003
Comments on draft labeling

OPDP, consulted by DCRP on April 4, 2014, has reviewed the proposed Package Insert (PI) and the Carton and Container Labeling for Prestalia (perindopril arginine and amlodipine) tablets for oral use (Prestalia).

OPDP's comments are provided directly on the attached copy of the proposed PI for Prestalia. Our comments are based on the proposed labeling emailed to us on December, 5, 2014.

OPDP does not have any comments on the proposed Carton and Container labeling for Prestalia at this time. Our review was based on the Carton and Container labeling emailed to us on December 11, 2014.

Thank you for the opportunity to review the proposed labeling for Prestalia.

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

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

ZARNA PATEL
12/12/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 12, 2014

To: Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products (DCRP)

Through: Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)
Marcia Britt Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): PRESTALIA (perindopril arginine and amlodipine)

Dosage Form and Route: tablets for oral use

Application Type/Number: NDA 205003

Applicant: Symplmed Pharmaceuticals, LLC

1 INTRODUCTION

On March 21, 2014, Symplmed Pharmaceuticals, LLC submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 205003 for PRESTALIA (perindopril arginine and amlodipine) tablets with the proposed indication for the treatment of hypertension.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Cardiovascular and Renal Products (DCRP) on April 4, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PRESTALIA (perindopril arginine and amlodipine) tablets.

2 MATERIAL REVIEWED

- Draft PRESTALIA (perindopril arginine and amlodipine) tablets PPI received on March 21, 2014 and June 18, 2014, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on December 5, 2014.
- Draft PRESTALIA (perindopril arginine and amlodipine) tablets Prescribing Information (PI) received on March 21, 2014 and June 18, 2014, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on December 5, 2014.
- Approved EDARBYCLOR (azilsartan medoxomil and chlorthalidone) tablets comparator labeling dated July 23, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

Patient Information
PRESTALIA® (pres-ta -li-ə)
(perindopril arginine and amlodipine)
tablets

Read this Patient Information before you start taking PRESTALIA and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about PRESTALIA?

- PRESTALIA can cause harm or death to your unborn baby.
- Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.
- If you become pregnant while taking PRESTALIA, tell your doctor right away. Your doctor may switch you to a different medicine to treat your high blood pressure.

What is PRESTALIA?

PRESTALIA is a prescription medicine that contains perindopril arginine, an angiotensin converting enzyme inhibitor (ACE inhibitor), and amlodipine, a calcium channel blocker.

PRESTALIA is used to treat high blood pressure (hypertension):

- when one medicine to lower your high blood pressure is not enough
- as the first medicine to lower your high blood pressure if your doctor decides you are likely to need more than one medicine

It is not known if PRESTALIA is safe and effective in children.

Who should not take PRESTALIA?

Do not take PRESTALIA if you:

- have a history of (b) (4) angioedema (b) (4)
Symptoms of angioedema may include swelling of your face, tongue or throat, trouble breathing, itching, hives or skin rash, and stomach (abdominal) pain.
- are allergic to perindopril, or any other ACE inhibitor medicine
- are allergic to amlodipine
- have diabetes and take a medicine that contains aliskiren

What should I tell my doctor before taking PRESTALIA?

Before you take PRESTALIA, tell your doctor about all of your medical conditions, including if you:

- have heart problems
- have liver or kidney problems
- have diabetes
- have been told that you have abnormal (b) (4) levels in your blood
- (b) (4)
- are vomiting or have diarrhea
- plan to have a surgical (b) (4) procedure
- (b) (4) r
- are pregnant or plan to become pregnant. See **“What is the most important information I should know about PRESTALIA?”**

- are breastfeeding or plan to breastfeed. It is not known if PRESTALIA passes into your breast milk. You and your doctor should decide if you will take PRESTALIA or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking PRESTALIA with other medicines can cause serious side effects.

Especially tell your doctor if you take:

- medicines for high blood pressure or heart problems
- water pills
- salt substitute
- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take PRESTALIA?

- Take PRESTALIA exactly as your doctor tells you.
- Take PRESTALIA 1 time each day.
- If you take too much PRESTALIA, call your doctor or go to the nearest emergency room right away.

What are the possible side effects of PRESTALIA?

PRESTALIA can cause serious side effects, including:

See **“What is the most important information I should know about PRESTALIA?”**

- **Serious allergic reactions that can be life threatening.** Stop taking PRESTALIA and get emergency medical help right away if you get any of these symptoms of a serious allergic reaction:
 - swelling of your face, lips, tongue, throat, arms, hands, legs, or feet
 - trouble swallowing
 - trouble breathing
 - stomach (abdomen) pain with or without nausea or vomiting

People who are black and take PRESTALIA have a greater risk of having a serious allergic reaction than people who are not black and take PRESTALIA.

- **Worsening of chest pain (angina) or a heart attack (myocardial infarction)** can happen after you start taking or increase your dose of PRESTALIA. Get emergency help if you get worse chest pain or chest pain that does not go away.

(b) (4)

- **Low blood pressure** (hypotension) is most likely to happen if you also:
 - take water pills (diuretics)
 - are on a low salt diet
 - are on kidney dialysis
 - have heart problems
 - have vomiting or diarrhea

If you feel faint or dizzy, lie down and call your doctor right away.

- **Increased amount of potassium in the blood.** Your doctor will check your potassium blood level during your treatment with PRESTALIA.

- **Cough.** This cough usually goes away after treatment with PRESTALIA is completed.
- **Kidney problems.** Some people with certain conditions may have kidney ^{(b) (4)} and may need to stop treatment with PRESTALIA. Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain.

(b) (4)

The most common side effects of PRESTALIA include:

- swelling of the feet, ankles, and hands
- cough
- headache
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of PRESTALIA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PRESTALIA?

- Store PRESTALIA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep PRESTALIA in a tightly closed container and in a dry place.

Keep PRESTALIA and all medicines out of the reach of children.

General information about PRESTALIA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PRESTALIA for a condition for which it was not prescribed. Do not give PRESTALIA to other people, even if they have the same symptoms that you have. It may harm them.

For more information, go to ^{(b) (4)}

What is high blood pressure (hypertension)?

Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too great.

High blood pressure makes the heart work harder to pump blood through the body and causes damage to the blood vessels. PRESTALIA can help your blood vessels relax so your blood pressure is lower. Medicines that lower your blood pressure may lower your chance of having a stroke or heart attack.

What are the ingredients in PRESTALIA?

Active ingredients: perindopril arginine and amlodipine besylate

Inactive ingredients: lactose, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate

This Patient Information has been approved by the U.S. Food and Drug Administration.

Marketed by:
SYMPLMED, LLC
Cincinnati OH 45227



Issued: [REDACTED] (b) (4)

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/s/

KAREN M DOWDY
12/12/2014

ZARNA PATEL
12/12/2014

MARCIA B WILLIAMS
12/12/2014

BARBARA A FULLER
12/12/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 22, 2014

TO: Aliza Thompson, Team Leader
Karen Hicks, Medical Officer
Wayne Amchin, Regulatory Health Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205003

APPLICANT: Symplmed Pharmaceuticals, LLC

DRUG: Xoma™ (perindopril arginine 14 mg; amlodipine besylate 10 mg)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: treatment of hypertension

PROTOCOLS:

Study X985400 (PATH): Perindopril Amlodipine for the Treatment of Hypertension: A Multicenter, Randomized, Double-Blind, Parallel Group Study Evaluating the Efficacy and Safety of a Fixed- Dose Combination of Perindopril Arginine Plus Amlodipine Besylate versus Perindopril Erbumine and Amlodipine Besylate in Subjects with Essential Hypertension.

Population: men or women between 18 to 75 years of age, inclusive, with hypertension defined as Diastolic Blood Pressure (DBP) ≥ 95 mm Hg and ≤ 115 mm Hg at Visit 2 (Day 0)

Study CL2-05985-00: Efficacy and Safety of the Fixed Oral Low-Dose Perindopril Arginine 3.5 mg/amlodipine 2.5 mg combination compared with each component (perindopril arginine 3.5 mg and amlodipine 2.5 mg) and with Perindopril Arginine 5 mg and amlodipine 5 mg.

Population: Men or women between the ages of 18 to 79 inclusive years old, with mild to moderate essential, uncomplicated hypertension defined as DBP between 95 and 110 mmHg and Systolic Blood Pressure (SBP) between 150 and **180** mmHg at Visit 2 (Day 0).

CONSULTATION REQUEST DATE: April 30, 2014

INSPECTION SUMMARY GOAL DATE: September 30, 2014 (if possible)

PDUFA DATE: January 21, 2015

I. BACKGROUND:

Symplmed Pharmaceuticals submitted NDA 205003, for XOMA 985, a fixed-dose combination of perindopril arginine and amlodipine besylate for the treatment of hypertension. Perindopril, an angiotensin-converting enzyme (ACE) inhibitor and amlodipine, a calcium channel blocker (CCB) have both been widely used as monotherapies, for more than fifteen years in countries worldwide. Both ACE inhibitors and CCBs lower blood pressure by reducing peripheral resistance. Cellular calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms, and the Applicant proposes that the combination may have a favorable synergistic effect for the treatment of essential hypertension.

The Applicant Symplmed submitted data from a Phase 3 clinical study (X985400 [PATH]) comparing the highest strength of the combination product to those of the highest strength of the individual components administered as monotherapies; and a Phase 2 study (CL2-05985-

005) comparing the effects of the lowest strength of the combination product with those of the individual components administered as monotherapies.

1) Study X985400 [PATH], was a Phase III, multicenter, randomized, double-blind, parallel-group trial that enrolled a total of 837 patients at 59 centers in the United States, in a 1:1:1 ratio to receive the fixed-dose combination of PERa/AMLb 14/10 mg once daily, AMLb 10 mg once daily, or PERe 16 mg once daily. The study design consisted of a screening visit, a 3-week washout period, and a 6-week double-blind treatment period. Baseline blood pressure was established using the average of three measurements taken at Visit 2 (Day 0) using the digital blood pressure monitor supplied by the Sponsor. The primary efficacy endpoint was the difference between the values for mean change from baseline to Visit 4 (Day 42/End of Treatment [EOT]) in mean seated trough cuff diastolic blood pressure (DBP) when comparing the treatment groups: PERa/AMLb 14/10 mg versus PERe 16 mg; and PERa/AMLb 14/10 mg versus AMLb 10 mg.

2) Study CL2-05985-005 was a Phase II study that used a factorial design to demonstrate that the perindopril arginine/amlo地平ine 3.5/2.5 mg combination was superior to monotherapy with perindopril arginine 3.5 mg and monotherapy with amlodipine 2.5 mg for both DBP and SPB. A total of 1,581 patients were randomized (248 patients in the Perindopril 3.5 mg/Amlodipine 2.5 mg group; 250 patients in the placebo group; 273 patients in the Perindopril 3.5 mg group; 274 patients in the Amlodipine 2.5 mg group; 272 patients in the Perindopril 5 mg group; and 264 patients in the Amlodipine 5 mg group) at 165 centers located in six countries including France, Russia, Ukraine, Lithuania, Hungary and Latvia. A total of 1497 patients completed the study. This study had an ambulatory blood pressure measurement (ABPM) sub-study which included 1297 patients.

The primary efficacy endpoint for the overall study was supine diastolic blood pressure (DBP), expressed as the change from baseline to last observation. The last observation value corresponded to the measure done the day following the last drug administration.

Reasons for Site Selection: The sites chosen for inspection all had large treatment effects for at least one comparison with the monotherapies. These sites also had relatively high enrollment. Site 3007 in Lithuania conducted the CL2-05985-005 Phase II study and also conducted the ABPM sub-study.

II. Results

Name of CI/Address	Protocol # and # of Subjects	Inspection Dates	Final Classification
Eddie Armas, M.D. Well Pharma Medical Research, Corp. 7000 Southwest 62 nd Avenue Suites 405 and 100 Miami, FL 33143	Study X985400 (PATH) Site 564 28 subjects	July 22 -24, 2014	NAI
Cynthia Strout, M.D. Coastal Carolina Research Center 1156 Bowman Road, Suite 102 Mount Pleasant, SC 29464	Study X985400 (PATH) Site 654 17 subjects	May 19-22, 2014	NAI
Barry C. Lubin, M.D. National Clinical Research, Norfolk, Inc. 885 Kempsville Road Suite 221 Norfolk, VA 23502	Study X985400 (PATH) Site 666 18 subjects	June 17- 24, 2014	NAI
Geri Eileen Poss, M.D. Paragon Research Center 1148 East Commerce St. San Antonio, TX 78205	Study X985400 (PATH) Site 578 15 subjects	June 25 – 27, 2014	NAI
Prof. Zaneta Petrulioniene Private Medical Center “Kardivita” Kolektyvo str. 13d Vilnius, Lithuania 08314	Study CL2-05985-005 (28 subjects enrolled) ABPM sub study (18 subjects enrolled) Site 3007	August 11 - 2014	Preliminary VAI (EIR pending)
Symplmed 5375 Medpace Way Cincinnati, OH 45227	Study X985400 (PATH)	July 8 – 11, 2014	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Eddie Armas, M.D. (Site 564)

Well Pharma Medical Research, Corp
7000 Southwest 62nd Avenue
Suites 405 and 100
Miami, FL 33143

a. What was inspected: Dr. Eddie Armas (Site 564) has 70 INDs in the COMIS database. Well Pharma Medical Research Corporation is a contract research organization (CRO), that is owned by Dr. Armas. Although Dr. Armas has no prior inspections, a BEQ inspection of the CRO was conducted in April/May 2014, and no significant deviations were observed.

At this site, 31 subjects were screened, 28 subjects enrolled, and 27 subjects completed the study. One subject terminated early by withdrawing consent.

The FDA field investigator reviewed source documents for 31 subjects for Informed Consent Document compliance and data listing verification; and sixteen subjects for protocol compliance including inclusion and exclusion criteria, primary efficacy endpoint, and adverse events. The source data verification consisted of laboratory results and clinical investigator observations. Drug accountability records and the monitoring log were also reviewed.

b. General observations/commentary: No deficiencies were found in the review of source records. No issues were identified during review of drug accountability records. The sponsor monitor conducted an adequate number of monitoring visits as reflected by the Site Visit Log. The regulatory file was well organized and captured correspondences and reports from the IRB. No deficiencies were observed, and no FDA-483 was issued.

c. Assessment of data integrity: The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

2. Cynthia Strout, M.D. (Site 654)

Coastal Carolina Research Center
1156 Bowman Road, Suite 102
Mount Pleasant, SC 29464

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Cynthia Strout has 110 INDs in the COMIS database and no prior inspections. Dr. Strout's site was chosen for inspection because of high enrollment and large treatment effects for at least one comparison with the monotherapies.

At this site, 32 subjects were screened, and seventeen subjects enrolled. Sixteen subjects completed the study.

The FDA field investigator reviewed study records for all seventeen enrolled subjects. The inspection corroborated the data listings with the source data. The field investigator reviewed the Informed Consent Documents for the 32 screened subjects. The field investigator reviewed all correspondence in the regulatory files, and drug accountability records.

b. General observations/commentary: No discrepancies were noted between source records and data listings. The primary efficacy endpoint was verifiable and there was no under reporting of adverse events. No deficiencies were noted in the review of informed consent documents. There were six monitoring visits in addition to a site initiation visit. No discrepancies were noted during the review of the regulatory files or the drug accountability records. No discrepancies were found during the inspection, and no FDA 483 was issued.

c. Assessment of data integrity: The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

3. Barry C. Lubin, M.D. (Site 666)

National Clinical Research, Norfolk, Inc.
885 Kempsville Road
Suite 221
Norfolk, VA 23502

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Barry Lubin has three INDs in the COMIS database and no prior inspections. This site was chosen for inspection because of relatively high enrollment and large treatment effect for at least one of the comparisons to the monotherapies.

At this site, 34 subjects were screened, and eighteen subjects randomized. A total of fifteen subjects completed the study. One subject did not return for the second visit and was dropped from the study; two subjects were dropped and discontinued participation due to pre-existing conditions that were exclusionary.

The FDA field investigator reviewed study records for all eighteen randomized subjects. The inspection verified adherence to the study protocol, and corroborated the data listings to the source data. The drug accountability records were reviewed.

b. General observations/commentary: The inspection found that all subjects met eligibility criteria, and there were no discrepancies between the source data and data listings with respect to the primary and secondary efficacy endpoints, and adverse events. Review of the test article accountability records did not disclose any discrepancies. The FDA field investigator observed one minor discrepancy for failing to follow protocol procedures: Subject 1002's final study Visit 4 was scheduled to occur on May 30, 2012, but was conducted on May 24, 2012 because of the Memorial Day Holiday. This was > 3 days outside the time window specified by the protocol.

This violation was documented and isolated, and unlikely to importantly impact the efficacy results of the study.

In general, only one minor discrepancy was found during the inspection, The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

4. Geri Eileen Poss, M.D. (Site 578)

Paragon Research Center
1148 East Commerce St.
San Antonio, TX 78205

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Geri Eileen Poss has 46 INDs in the COMIS database and no prior inspections. This site was chosen for inspection because of relatively high enrollment and large treatment effect for at least one of the comparisons to the monotherapies.

At this site, 23 subjects were screened, and fifteen subjects randomized. Fourteen subjects completed the study. Subject #578-1015 withdrew from the study on May 1, 2012, following an unscheduled follow-up appointment due to adverse events of pedal edema and fatigue. The field investigator found that the reason for withdrawal of this subject was not documented in the source data, but had been entered in the electronic CRF and noted in the data listings. This item was discussed verbally with Dr. Poss at the end of the inspection.

The FDA field investigator reviewed study records for all fifteen randomized subjects. The inspection verified adherence to the study protocol, and corroborated the data listings to the source data.

b. General observations/commentary: Dr. Poss as Clinical Investigator identified herself as the most responsible person and maintained oversight over the study. The inspection found that all subjects met eligibility criteria, and there were no discrepancies between the source data and data listings with respect to the primary and secondary efficacy endpoints, and adverse events. Review of the test article accountability records did not disclose any discrepancies.

c. Assessment of data integrity: In general, no discrepancies were found during the inspection, and no FDA 483 was issued. The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

5. Dr. Zaneta Petrulioniene (Site 3007)

Kolektyvo str. 13d
Vilnius, Lithuania 08314

a. What was inspected: This inspection was performed as NDA 205003 [perindopril arginine 14 mg; amlopidine besylate 10 mg], and audited Study CL2-05985-005. Dr.

Zaneta Petrulioniene has 70 INDs in the COMIS database and no prior inspections. This site had relatively high enrollment and a large treatment effect for at least one comparison with the monotherapies. Dr. Petulioniene's site conducted the ambulatory blood pressure measurement (ABPM) sub-study used to support approval of this NDA.

Dr. Petrulioniene did not sign an FDA 1572 Statement of Investigator, but did sign a Clinical Investigator Agreement.

At this site, 37 subjects were screened, 28 subjects randomized and 25 subjects completed the CL2-05986-005 study. A total of 18 subjects entered the ABPM sub-study. The FDA field investigator corroborated the data listings with the subject records for the primary and secondary efficacy endpoints (twenty subjects for supine BP and ten subjects for standing BP); adverse events for all subjects; random checks of concomitant medications, serum chemistry, hematology, urinalysis and glycemia values. The field investigator compared the ABPM data with the ABPM reports on file at the site for ten of eighteen subjects.

b. General observations/commentary: The FDA field investigator corroborated the data listings with the subject records and observed no discrepancies with respect to primary and secondary efficacy endpoints. There were no discrepancies during the random checks of concomitant medications, serum chemistry, hematology, urinalysis and glycemic values. There were no discrepancies between ABPM data listings with ABPM reports on file.

At the end of the inspection, an FDA 483 was issued citing the following regulatory violations:

1. An investigation was not conducted according to the investigational plan. Specifically,

- a. The ancillary ABPM study attached to Protocol CL2- 05985-005 states the following at Week 8:
 - One or 2 days before visit W8, the study treatment dose will be taken immediately after the start of the recording.
 - If the recording ends one day before visit W8, the last study treatment dose will be taken after the end of the recording.
 - If the recording ends at visit W8, the patient will not take any study treatment this day (except if a repeat ABPM is needed).

The inspection found that two subjects were administered study drug the same day the ABPM device was removed at W8.

- i. For Patient 837: Progress notes dated 3/19/08 document the last intake of investigational product occurred at 10:10 am even though the ABPM recording ended at 9:42 am on 3/19/08. The patient should not have taken any study medication on 3/19/08. A repeat ABPM was not necessary.

- ii. 2. For Patient 1315: The CRF and progress notes document W8 occurred on 6/10/08 and the ABPM device was removed on 6/10/08 at 9:23 am. The CRF documents the last intake of study treatment occurred on 6/10/08 at 9:23 am. The patient should not have taken any study medication on 6/10/08. A repeat ABPM was not necessary.

The above violations did not significantly impact data reliability for the ABPM sub-study.

- b. Patients were to receive the same therapeutic unit number at Week 0 (P1) and Week 4 (P2). Two patients did not receive the same therapeutic unit number:
 - i. Patient 00552- This patient received therapeutic unit number 052624 at Week 0 and therapeutic unit number 052631 at Week 4. This led to a treatment group change for this subject from Perindopril 3.5 mg at Week 0 (9/12/2007) to placebo at Week 4 (10/10/2007).
 - ii. 2. Patient 00595- This patient received therapeutic unit number 052631 at Week 0 (Perindopril) on 10/8/2007, and therapeutic unit number 050021 (placebo) at Week 4 on 11/12/2007. This subject was reportedly excluded from the per protocol analysis.

The above violations were reported as protocol violations which appear in the data listings for the study.

2. Investigational drug disposition records are not adequate with respect to use by subjects. Specifically,

- a. The Recovery and Destruction Form of Therapeutics Units (RDFTU) documents Patient 00595 returned 13 units of Kit 052631 for P2, whereas Kit 052631 was dispensed to Patient 00552.
- b. The RDFTU documents P1 and P2 of Kit 050021 were lost. However, the Therapeutic Units Tracking Form (TUTF) documents Kit 050021 was dispensed to Patient 00595 for P2.
- c. The TUTF documents Kits 061621, 051758, and 057074 were lost.

In her response letter dated September 4, 2014, Dr. Petrulioniene states that these kits were lost after being received and before storage in the locked cupboard and locked storage room. These losses were then documented on the Recovery and Destruction Form (RDFTU). Dr. Petrulioniene's response is acceptable.

- d. The RDFTU documents destruction of units for the following units that were documented in the destruction log were not entered in the TUTF as being dispensed to the individual patients:

- Patient 00488- Units from Kit 062203
- Patient 00483- Units from Kit 058390
- Patient 1315- Units from Kit 050479
- Patient 2032- Units from Kit 056537
- Patient 1306- Units from Kit 060290
- Patient 2034- Units from Kit 056984

3. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically,

a. The ABPM sub-study protocol, under Section 8.6, Source Data, states “one hard copy of the ABPM recordings will be sent by Medifacts to the investigator. This copy will be locally archived with the original recordings and considered as source document”.

The original recordings were not available for review, and as a result, the field investigator was unable to verify or confirm the raw data contained in the Medifacts ABPM recordings.

In her response letter dated September 4, 2014, Dr. Petrulioniene states it is not possible to read ABPM data without a specific software program, which had been supplied by Medifacts to the site during the study. The ABPM equipment had been returned to Medifacts at the end of the study. Although floppy disks were used as back-up in case of laptop failure, Medicom research software was still required to read those data.

c. Assessment of data integrity: Although regulatory violations were found for the CL2-05985-005 study, and the APBP sub-study, they are minor and isolated and unlikely to significantly impact data integrity. The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

6. Symplmed (Sponsor)

5375 Medpace Way
Cincinnati, OH 45227

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. XOMA Ltd. was the original sponsor for this study; this trial was completed under XOMA Ltd. in 2012. Symplmed inherited all contractual agreements related to this study from XOMA in June 2013. Symplmed is considered a virtual pharmaceutical company.

The inspection assignment requested a focus on four domestic clinical investigator sites for the PATH study: Site #564 (Armas, 27 subjects), Site #654 (Strout, 17 subjects), Site #666 (Lubin, 16 subjects), Site #578 (Poss, 15 subjects); and one foreign site for the CL2-- 05985-005 and ABPM sub-study: Site #3007 (Petrulioniene, 18 subjects).

During the inspection, the FDA field investigator reviewed the following: FDA Forms 1572's and financial disclosure statements for the 59 clinical investigators used in this study; training and qualification of monitors; monitoring records for ten clinical sites;

quality assurance audit certificates; SOPs for adverse event reporting, data collection and data management; and test article accountability records. No comparisons were made of the source documents to the data listings during this inspection.

b. General observations/commentary:

Monitoring was conducted by Medpace, a CRO. No deficiencies were noted with respect to monitoring or the above reviews. No significant observations were observed during the inspection, and no FDA form 483 was issued.

c. Assessment of data integrity: The study was conducted well and no deficiencies were observed at the sponsor's site. OSI recommends that the data is acceptable in support of the claimed indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four domestic clinical investigator inspections and a Sponsor site inspection were conducted in as a data audit of the PATH study; one foreign inspection was conducted as a data audit of the CL2--05985-005 and ABPM sub-study for NDA 205003. No regulatory violations were found during the inspections of the four domestic sites, all of which conducted the PATH study [Armas (Site 564), Strout (Site 654), Lubin (Site 666), Poss (Site 578)]. These domestic inspections were classified as NAI. No regulatory violations were found during the inspection of the applicant/sponsor Symplmed, and that inspection was classified NAI. Regulatory violations were found during the inspection of Site 3007 (Zaneta Petrulionliene, Lithuania) who conducted Study CL2-05985-005 and ABPM sub-study. The regulatory violations related to inadequate and inaccurate drug accountability records, failure to adhere to the investigational plan; and inadequate and inaccurate records during the study.

Although regulatory violations were noted at Site 3007 in Lithuania, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable.

Note: The final EIR for Dr. Zaneta Petrulionliene (Site 3007, Lithuania) was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
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/s/

SHARON K GERSHON
09/22/2014

SUSAN D THOMPSON
09/22/2014

KASSA AYALEW
09/22/2014

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: July 16, 2014
Requesting Office or Division: Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number: NDA 205003
Product Name and Strength: Prestalia (Perindopril arginine/Amlodipine besylate) Tablets,
3.5 mg/2.5 mg, 7 mg/5 mg, 14 mg/10 mg
Product Type: Multi-Ingredient
Rx or OTC: RX
Applicant/Sponsor Name: Symplmed Pharmaceuticals Inc.
Submission Date: March 21, 2014
OSE RCM #: 2014-652
DMEPA Primary Reviewer: Janine Stewart, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label and Prescribing Information for Prestalia (Perindopril arginine/Amlodipine besylate) Tablets for areas of vulnerability that can lead to medication errors in response to a request from the Division of Cardiovascular & Renal Products (DCRP).

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.

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed prescribing information (PI) and container labels to identify deficiencies that may lead to medication errors and areas for improvement.

After careful review of the full prescribing information, we note the inconsistency of nomenclature for perindopril and amlodipine. We note the inconsistency of the storage temperature information between the How Supplied section of the proposed PI labeling and on the side panel of the container label. Additionally, we note the absence of the unit of measure in the expression of the perindopril arginine strength for each of the 3 fixed-dose Perindopril products throughout the insert labeling. Furthermore, we note opportunities to improve the readability and the prominence of important product information on the container label. Thus, we provide recommendations to mitigate confusion and promote the safe use of this product in Section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product.

4.1 COMMENTS FOR THE DIVISION

Based on this review, we have revised the proposed Prescribing Information as detailed below for review and consideration by DCRP.

General Comment

1. We note the presentation of the established name on the proposed container label is without parenthesis. We defer to CMC for the appropriate established name expression.
2. There is inconsistent nomenclature used throughout the PI for perindopril (i.e. perindopril arginine, perindopril) and amlodipine (i.e. amlodipine besylate, amlodipine). We defer to CMC for the correct nomenclature to be used for these two entities throughout the PI and on the container label.

Prescribing Information (PI)

1. In the *Highlights of Prescribing* section and throughout the PI, add the unit of measure after each corresponding number in the strength expressions for each the 3 fixed-dose Perindopril products.
2. Please see Appendix H for additional comments on the PI.

4.2 RECOMMENDATIONS FOR THE APPLICANT

General Comment

1. Revise the storage temperature statements so that they are consistent between the prescribing information and the container labels.

Container Labels

1. Revise the presentation of the established name so it is printed in letters that are at least half as large as the letters comprising the proprietary name, and the prominence of the established name should have a prominence commensurate with the prominence with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).

2. Revise the strength expression so each of the three proposed strengths is presented with adequate spacing, for example revise to “7 mg/5 mg” (instead of “7mg/5mg”) throughout the principal display panel and the side panel. Additionally, revise the presentation of the strength statement with different color bars to highlight the strength expressions to aid the differentiation of each of the three strengths.
3. Minimize the ‘Rx Only’ statement on the principal display panel (PDP) so it does not compete with the prominence of other important product information on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Prestalia that Symplmed submitted on March 21, 2014.

Table 2. Relevant Product Information for Prestalia	
Active Ingredient	perindopril arginine/amlodipine besylate
Indication	For the treatment of hypertension (b) (4) [REDACTED]
Route of Administration	Oral
Dosage Form	Immediate- release tablet
Strength	3.5 mg/2.5 mg, 7 mg/5 mg, 14 mg/10 mg
Dose and Frequency	Starting dose: 3.5 mg/2.5 mg by mouth once daily (b) (4) [REDACTED] The maximum recommended dose is 14 mg/10 mg by mouth once daily.
How Supplied	(b) (4) count bottles for all strengths. (b) (4) [REDACTED]
Storage	Controlled room temperature of (b) (4) 25°C ((b) (4) 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F).
Container Closure	100 mL, (b) (4), white, high density polyethylene (HDPE), wide mouth round bottles and capped (b) (4) [REDACTED] closure with an induction seal. Each bottle also contains a polyester pharmaceutical coil and a 1 gram silica gel desiccant canister.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Dive on May 15, 2014 using the terms, Prestalia to identify reviews previously performed by DMEPA.

C.2 Results

- **OSE RCM# 2013-16650 and 2014-17141, dated April 14, 2014**

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 Prestalia labels and labeling submitted by Symplmed on March 21, 2014.

- Container labels
- Prescribing Information (Appendix H)

G.2 Label and Labeling Images



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

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APPENDIX H. FULL PRESCRIBING INFORMATION

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/s/

JANINE A STEWART
07/16/2014

CHI-MING TU
07/16/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205003 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Prestalia Established/Proper Name: Perindopril arginine/Amlodipine besylate fixed-dose combination Dosage Form: Tablet Strengths: 3.5/2.5 mg, 7/5 mg, and 14/10 mg		
Applicant: Symplmed Pharmaceuticals, LLC (Symplmed) Agent for Applicant (if applicable): Medpace, Inc		
Date of Application: 3-21-2014 Date of Receipt: 3-21-2014 Date clock started after UN:		
PDUFA Goal Date: 1-21-2015		Action Goal Date (if different):
Filing Date: 5-20-2014		Date of Filing Meeting: 5-5-2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): treatment of hypertension		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 </i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 108233				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input type="checkbox"/>	X		Proprietary Name Prestalia Granted, letter in DARRTS on 4/22/14
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	DARRTS shows this as a 505(b)(1), and the document room has been asked to correct this.
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	X		
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	X	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) X All electronic <input type="checkbox"/> Mixed (paper/electronic) X CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X	<input type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	X	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): A pre-NDA meeting was scheduled for November 4, 2013. Meeting Preliminary Comments were sent to the sponsor and the sponsor submitted clarifying questions in advance of the meeting. The sponsor requested cancellation of the pre-NDA meeting based on the Meeting Preliminary Comments and DCRP's response to the clarification questions.	X	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 5-20-14

NDA: 205003

PROPRIETARY NAME: Prestalia

ESTABLISHED/PROPER NAME: XOMA 985, a fixed-dose combination of perindopril arginine and amlodipine

DOSAGE FORM/STRENGTH: 3.5/2.5 mg, 7/5 mg, and 14/10 mg tablets

APPLICANT: Symplmed Pharmaceuticals, LLC (Symplmed)

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of hypertension

BACKGROUND: Symplmed Pharmaceuticals LLC submitted NDA 205003, Prestalia (Perindopril arginine/Amlodipine besylate) tablets, a fixed dose combination of Perindipril, an ACE inhibitor and Amlodipine besylate, a calcium channel blocker, under the 505(b)(2) regulatory pathway at three dose strengths for the treatment of hypertension, alone or with other antihypertensive agents. Symplmed is proposing to rely on two studies, X985400 (PATH) and CL2-05985-005 (conducted in Europe), comparing the proposed combination product with the monotherapies. A pre-IND meeting was held with the previous sponsor on October 20, 2010. The IND was received on August 4, 2011, and there were no hold issues. At the time, there was some discussion regarding the rationale for why the sponsor is changing the perindopril salt. It was suggested that the change was due to the arginine salt having greater stability, and Perindopril arginine is marketed outside the United States. Subsequently CMC clarified that Perindopril arginine salt has been chosen since its use led to better tableting performance compared to tertbutylamine salt. There was also some discussion at the time about potential genotoxic impurity in [REDACTED] (b) (4)

[REDACTED] CMC, nonclinical, clinical, and statistical comments were conveyed to the sponsor on September 21, 2011, and comments on the statistical analysis plan were conveyed on July 23, 2012. On October 14, 2012, the sponsor requested a meeting on biowaiver issues, and DCRP issued a written response only to the questions on November 13, 2012. The IND was inactivated on March 18, 2013. On August 20, 2013, there was a change in sponsor to the current sponsor, and the request for the current meeting was submitted on September 20, 2013. The pre-NDA meeting was scheduled for November 4, 2013, but the Meeting Preliminary Comments and subsequent clarification on some points, led to the sponsor agreeing that the meeting was not necessary.

The NDA was submitted on March 21, 2014. A user fee waiver was granted by ORP. The PDUFA date is January 21, 2015. The filing meeting was held on May 5, 2014, and the filing date is May 20, 2014. A team meeting is scheduled for June 2, 2014, and the mid-cycle meeting is scheduled for August 27, 2014. Clinical, nonclinical, statistical, and clinical pharmacology IRs have been issued to date.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Wayne Amchin	Yes
	CPMS/TL:	Ed Fromm	N
Cross-Discipline Team Leader (CDTL)	Aliza Thompson		Y
Clinical	Reviewer:	Karen Hicks	Y
	TL:	Aliza Thompson	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:	Brian Riley (Acting)	N

Clinical Pharmacology	Reviewer:	Peter Hinderling	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Jialu Zhang	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Baichun Yang	Y
	TL:	Tom Papoian	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Charles Jewell	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:	Brian Riley (Acting)	N
CMC Labeling Review	Reviewer:	Charles Jewell	Y
	TL:	Kasturi Srinivasachar	Y
Facility Review/Inspection	Reviewer:	Vibhakar Shah	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Janine Stewart	Y
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Pharmacovigilance	Reviewer:	Amy Chen	N

Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Biopharm	Reviewer: Sandra Suarez TL: Angelica Dorantes		Y N
OPDP	Reviewer: Zarna Patel		Y
Patient Labeling	Reviewer: Karen Dowdy RPM: Dorch Brantley		Y N
OSE RPM	Karen Bengston		Y
Environmental Specialist	James Laurenson		N
Other attendees Associate Director, Regulatory Affairs, ODE I	Colleen Locicero		Y
Associate Director for Labeling, DCRP (Detail)	Michael Monteleone		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p> <p>Applicant’s bridge to support reliance on Aceon and Norvasc (use of products other than Aceon and Norvasc in BA/BE study and basis for cross-comparison based on information in the Norvasc and Aceon NDAs but not in the Norvasc and Aceon labels.</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? 	<p>X YES</p> <p><input type="checkbox"/> NO</p>

If no, explain:	
<ul style="list-style-type: none"> Electronic Submission comments List comments:	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	X Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	X Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	X Review issues for 74-day letter
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
If no , was a complete EA submitted?	X YES <input type="checkbox"/> NO
If EA submitted , consulted to EA officer (OPS)?	X YES <input type="checkbox"/> NO
Comments:	

<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: This submission is acceptable from a product quality microbiology standpoint and will be recommended for approval. Therefore, no product quality microbiology reviewer assignment will be made for this submission. A review memo describing the assessment of the microbial controls for the drug product will be entered into DARRTS.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments: Both container labels and the PI need to be revised since the strength of amlodipine corresponds to the free base and not the salt, amlodipine besylate. An equivalency statement should also be included separately on the container labels.</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Norman Stockbridge, M.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): August 27, 2014</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review

ACTIONS ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

WAYNE S AMCHIN
05/20/2014

AGREED INITIAL PEDIATRIC STUDY PLAN

For

XOMA 985

Symplmed Pharmaceuticals, LLC

5375 Medpace Way
Cincinnati, OH 45227

Tel: 888-552-9769 x101

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin converting-enzyme
CCB	calcium channel blocker
DBP	diastolic blood pressure
SBP	systolic blood pressure

1 OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION

Hypertension affects approximately 1 billion individuals worldwide. As the population ages, the prevalence of hypertension will increase even further. Hypertension is a major independent risk factor for atherosclerotic vascular diseases. Epidemiologic evidence clearly and definitively demonstrates that the relationship between blood pressure and risk of cardiovascular events is graded and continuous, and blood pressure reduction is effective in reducing this risk. Despite this evidence, current control rates of hypertension remain far below the Healthy People 2010 goal of 50%. Approximately 30% of patients are unaware they have hypertension, only 60% are being treated, and only 30% are treated to a target goal of systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg.

The definition of hypertension in children and adolescents is an average SBP and DBP that is greater than or equal to the 95th percentile for sex, age, and height on at least three separate occasions (Falkner, 2005). Severe symptomatic hypertension occurs uncommonly in children. Additionally, while many drugs are available for adults for the treatment of severe hypertension, few of these drugs have been studied in children (Flynn, 2009).

The prevalence of hypertension among children has increased in direct relation to the increase in childhood obesity. In the past, most cases of hypertension in children were thought to be secondary to another underlying disease. Over the last 15 years, an increasing percentage of cases of pediatric hypertension are considered primary, and associated with obesity (Flynn, 2009).

Weight reduction is the primary therapy for obesity-related hypertension in children and prevention of excess weight gain will limit further blood pressure increases later in life (Faulkner, 2005).

Many adults remain on antihypertensive medication for their entire lives. There is abundance clinical trial evidence with antihypertensive agents across mechanistic classes supporting safety, efficacy, and long term benefits of treatment to control blood pressure in adults. Clinical trial data are more limited among children (Faulkner, 2005). In addition, standard treatment of pediatric hypertension is with single agents, and there is little pediatric experience with combination therapy for hypertension.

Finally, and more specifically, routine use of fixed-dose combination products for the treatment of hypertension in children is not recommended (Faulkner, 2005).

2 OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT

A New Drug Application (NDA) for XOMA 985 is being submitted for the fixed-dose combination of perindopril arginine and amlodipine besylate. Perindopril, an angiotensin converting-enzyme (ACE) inhibitor, is approved by the FDA in ACEON[®], as the erbumine salt, and amlodipine besylate, a calcium channel blocker (CCB) is the active ingredient in the FDA approved drug, NORVASC[®]. The proposed indication for XOMA 985 is for the treatment of essential hypertension, alone or with other antihypertensive agents.

Perindopril, in this product as an arginine salt, is an ACE inhibitor used for the treatment of

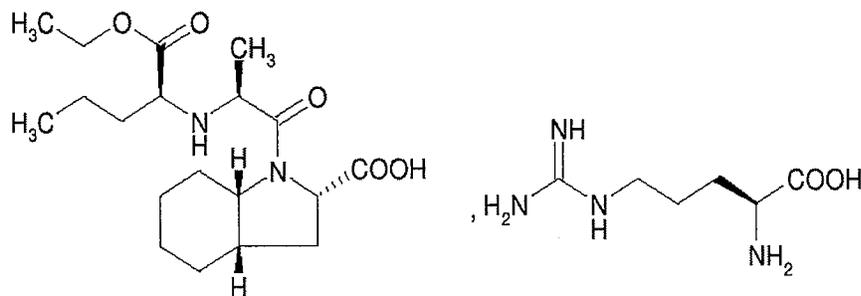
hypertension, heart failure, and for patients with coronary artery disease. Perindopril acts via its active metabolite, perindoprilat.

The chemical name of perindopril arginine is L-arginine (2S,3aS,7aS)-1- [(2S)-2-[(1S)-1-(ethoxycarbonyl)butyl]amino] propanoyl] octahydro-1*H*-indole-2-carboxylate.

The empirical formula of perindopril arginine is C₁₉H₃₂N₂O₅, C₆H₁₄N₄O₂ and its molecular weight is 542.7 (salt form) or 368.5 (free amino acid).

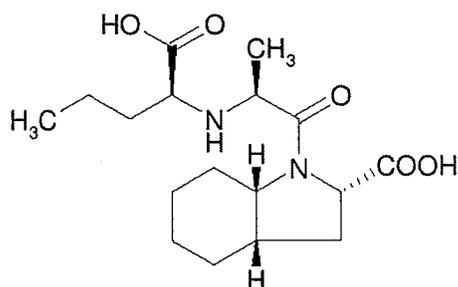
The chemical structures for the arginine salt and the active metabolite are shown below:

Perindopril arginine:



Chemical Name:	L-arginine (2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butyl]amino] propanoyl] octahydro-1 <i>H</i> -indole-2-carboxylate
Molecular Weight:	542.7 (salt form) or 368.5 (free acid)
Molecular Formula:	C ₁₉ H ₃₂ N ₂ O ₅ , C ₆ H ₁₄ N ₄ O ₂
CASRN:	82834-16-0

Perindoprilat:



Chemical Name:	(2S,3aS,7aS)-1-((S)-N-((S)-1-Carboxybutyl)alanyl)hexahydro-2-indolinecarboxylic acid
Molecular Weight:	340.42
Molecular Formula:	C ₁₇ H ₂₈ N ₂ O ₅
CASRN:	95153-31-4

antihypertensives, particularly ACE inhibitors, as well as other factors related to the nature of a fixed-dose form, XOMA 985 does not present a *meaningful therapeutic benefit* over existing therapies and *is not likely to be used in a substantial number of patients*. Accordingly, Symplmed proposes that XOMA 985 meets the requirements for a full pediatric waiver.

XOMA 985 does not present a *meaningful therapeutic benefit* because it does not represent an improvement in the treatment, diagnosis, or prevention of a disease compared with marketed products adequately labeled for use in the relevant pediatric population. A combination of convenience offers no meaningful therapeutic benefit over the approved individual component products within the combination. Choices of antihypertensive drugs available to children are similar to the choices available to adults; however, the doses for children are often smaller. Accordingly, great care must be taken to adjust the doses in this population to avoid adverse reactions (Chobanian, 2003). Although the standard regimen for the treatment of hypertension in a pediatric population can include adding a complementary agent, the potential side effects associated with incorrectly adjusting the dose and the resulting need for flexibility of dosing suggest that the prescription of monotherapies better meets the safety and efficacy profile of the pediatric hypertensive population (Stephens, 2012). As such, XOMA 985, as a fixed-dose combination, does not represent *an improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population*.

Furthermore, XOMA 985 is not in a class of products or for an indication for which there is a need for additional options. There are several ACE inhibitors, including enalapril, captopril, lisinopril, fosinopril, quinapril, benazepril, and ramipril, for which there is FDA approved labeling for the pediatric population (Stephens, 2012; Daniels et al., 2012). Additionally, Epaned™ (enalapril maleate Powder for Oral Solution) was recently approved by the FDA for the treatment of hypertension (high blood pressure) in patients 1 month of age and older. Amlodipine, the CCB in XOMA 985, also has FDA-approved labeling indicating that it is safe and effective in children over 6 years. (For a more comprehensive list of pediatric clinical studies conducted to date, see Daniels, 2012, Chapter 8 and US FDA, Pediatric Science and Research Activities, 2013.)

In addition to not providing a *meaningful therapeutic benefit over existing therapies for pediatric patients*, XOMA 985 also will not be *used in a substantial number of pediatric patients*. First, XOMA 985 is a fixed-dose combination, and, as noted above, monotherapies provide the required dosing flexibility for the pediatric hypertension population. Furthermore, there are already several monotherapies that have been studied in a pediatric population, including several ACE inhibitors and amlodipine; amlodipine is attractive as a monotherapy for pediatric hypertensive patients because it is a suspension and has a longer half-life than most CCBs (Sahney, 2006). It is more likely that monotherapies that have been studied in a pediatric population would be prescribed for essential hypertension. It is also likely that an ACE inhibitor that has already been studied in the pediatric population, as opposed to perindopril or a fixed-dose combination with perindopril, which has not been studied in the pediatric population, would be prescribed for patients with severe hypertension due to the renal disease that often underlies severe hypertension in the pediatric population (Flynn, 2009). The pediatric population appears to have an exaggerated response to ACE inhibitors, including the potential for prolonged

hypotension with oliguric renal failure in infants (Blowey, 2002). In addition, neutrophilic hypersegmentation has been observed with enalapril or captopril in children aged 2-16 years (Okutan, 2008), and a diminished hypertensive effect with ACE inhibitors as a class overall has been observed in black children as compared to white children (Li, 2008). Thus, evidence from the published literature and current practice support the need to prescribe an ACE inhibitor that has already been studied as a monotherapy in the pediatric population.

Accordingly, based on the regulatory standard that must be met, as well as literature in the public realm, a full waiver for XOMA 985 is being requested as XOMA 985 does not present a *meaningful therapeutic benefit over existing therapies for pediatric patients and the article is not likely to be used in a substantial number of pediatric patients.*

5 SUMMARY OF PLANNED NONCLINICAL AND CLINICAL STUDIES

Not Applicable

6 PEDIATRIC FORMULATION DEVELOPMENT

Not Applicable

7 NONCLINICAL STUDIES

Not Applicable

8 CLINICAL DATA TO SUPPORT DESIGN AND/OR INITIATION OF STUDIES IN PEDIATRIC PATIENTS

Not Applicable

9 PLANNED PEDIATRIC CLINICAL STUDIES

9.1 Pediatric Pharmacokinetic Studies

Not Applicable

9.2 Clinical Effectiveness and Safety Studies

Not Applicable

10 TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN

Not Applicable

11 PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES

Not Applicable

12 AGREEMENTS FOR OTHER PEDIATRIC STUDIES

Not Applicable

13 REFERENCE LIST

The Pediatric Research Equity Act (PREA), 21 USC §355c (2003) (as reauthorized and amended by Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 402 (2007)). Available at: <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec355c.htm>. Accessed October 31, 2013.

Blowey D. Safety of the newer antihypertensive agents in children. *Exper Opin Drug Saf*. 2002;1(1):39-43.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. December 2003. Available at: <http://www.nhlbi.nih.gov/guidelines/hypertension/>. Accessed September 20, 2013.

Daniels SR, Benuck I, Christakis DA, Dennison BA, Gidding SS, Gillman MW, et al; National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents – Full Report. October 2012. Specifically Chapter 8, Table 8-5. Available at: http://www.nhlbi.nih.gov/guidelines/cvd_ped/. Accessed September 20, 2013.

Falkner B, Daniels SR, Flynn JT, Gidding S, Green LA, Ingelfinger JR, et al; National Heart, Lung, and Blood Institute. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. May 2005. Available at: http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf. Accessed September 20, 2013.

Flynn JT, Tullus K. Severe Hypertension in Children and Adolescents: Pathophysiology and Treatment. *Pediatric Nephrology*. 2009;24:1101-1112.

Li J, Baker-Smith C, Smith P, et al. Racial difference in blood pressure response to angiotensin-converting enzyme inhibitors in children: a meta-analysis. *Clin Pharmacol Ther*. 2008;84(3):315-9.

Okutan V, Kürekçi A, Sarici S, et al. Neutrophil hypersegmentation in children receiving angiotensin converting enzyme inhibitors. *Turks J Pediatr*. 2008;50(5)438-42.

Sahney S. A review of calcium channel antagonists in the treatment of pediatric hypertension. *Paediatr Drugs*. 2006;8:357-373.

Silvergate Pharmaceuticals, Inc. FDA Approves Epaned, a Liquid Form of Enalapril for Children and Adults. August 13, 2013. Available at: <http://www.silvergatepharma.com/fda-approves-epaned-a-liquid-form-of-enalapril-for-children-and-adults/>. Accessed October 2, 2013.

Stephens MM, Fox BA, Maxwell L. Therapeutic Options for the Treatment of Hypertension in Children and Adolescents. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine*. 2012;6:13-25.

United States Food and Drug Administration. Pediatric Science and Research Activities. March 18, 2013. Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106614.htm>. Accessed September 20, 2013.

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission*.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Plan – A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

Pediatric Population/Patient- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

PREA Pediatric Record/Pediatric Page – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

NDA#:205003

PRODUCT PROPRIETARY NAME: Prestalia ESTABLISHED/GENERIC NAME: Perindopril arginine/Amlodipine besylate

APPLICANT/SPONSOR: Symlmed Pharmaceuticals, LLC

PREVIOUSLY APPROVED INDICATION/S:

- (1) _____
- (2) _____
- (3) _____
- (4) _____

PROPOSED INDICATION/S:

- (1) *Treatment of Hypertension*
- (2) _____
- (3) _____
- (4) _____

NDA STAMP DATE: March 21, 2014

PDUFA GOAL DATE: January 21, 2015

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):
NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?

Did the sponsor submit an Agreed iPSP? Yes No

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes No

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)
Yes No

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes No
If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes No

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change.
If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.
- Pediatric Record

1. Pediatric age group(s) to be waived: Full Waiver.
2. Reason(s) for waiving pediatric assessment requirements (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)
 - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
 - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
 - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)
3. Provide justification for Waiver:

Prestalia is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not treated with combination antihypertensives (supported by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, Pediatrics 2004;114:555-576).

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*
The Division's language will likely be similar to the applicant's.

Potential language:

The safety and effectiveness of PRESTALIA in pediatric patients have not been established.

Neonates with a history of in utero exposure to PRESTALIA:

If oliguria or hypotension occurs, support blood pressure and renal function. Exchange transfusions or dialysis may be required.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis	cancer (continued):
adjunctive treatment of major depressive disorder	follicular lymphoma
age-related macular degeneration	gastric
Alzheimer's disease	hairy cell leukemia
amyloidosis	hepatocellular
amyotrophic lateral sclerosis	indolent non-Hodgkin lymphoma
androgenic alopecia	lung (small & non-small cell)
atherosclerotic cardiovascular disease	multiple myeloma
autosomal dominant polycystic kidney disease (ADPKD)	oropharynx (squamous cell)
benign monoclonal gammopathy	ovarian (non-germ cell)
benign prostatic hyperplasia	pancreatic
cancer:	prostate
basal cell and squamous cell skin cancer	refractory advanced melanoma
bladder	renal cell
breast	uterine
cervical	chronic lymphocytic leukemia
colorectal	chronic obstructive pulmonary disease
endometrial	cryoglobulinemia
esophageal	diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. Age groups included in the deferral request:
2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)*
 - a. Adult studies are completed and ready for approval
 - b. Additional safety or effectiveness data needed (describe)
 - c. Other (specify)
4. Provide projected date for the submission of the pediatric assessment (deferral date):
5. Did applicant provide certification of grounds for deferring assessments? Yes No
6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? Yes No
2. Does the division agree with the sponsor's plan? Yes No
3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? Yes No
 - a. Protocol Submission:

<p>b. Study Completion:</p> <p>c. Study Submission:</p> <p>4. Has a Written Request been issued? <input type="checkbox"/> Yes <input type="checkbox"/> No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)</p> <p>5. Has a PPSR been submitted? <input type="checkbox"/> Yes <input type="checkbox"/> No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)</p>
<p><i>Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.</i></p>
<p>DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL</p> <p><i>Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.</i></p>
<p>Types of Studies/Study Design:</p>
<p>Nonclinical Studies:</p>
<p>Clinical Studies:</p>
<p>Age group and population (indication) in which study will be performed: This section should list the age group and population exactly as it is in the plan.</p> <p><i>Example:</i> <i>Study 1: patients aged X to Y years.</i> <i>Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.</i></p>
<p>Number of patients to be studied or power of study to be achieved: <i>Example:</i></p>

Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female..*

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example :baseline, week 1, 4, and 6

<p>Statistical information (statistical analyses of the data to be performed):</p> <p><i>Example:</i> <i>Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.</i></p> <p><i>Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.</i></p> <p>Division comments on product safety: <i>Are there any safety concerns currently being assessed?</i> <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><i>Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies?</i> <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><i>Will a DSMB be required?</i> <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><i>Other comments:</i></p> <p>Division comments on product efficacy:</p> <p>Division comments on sponsor proposal to satisfy PREA:</p>
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PeRC ASSESSMENT TEMPLATE

Please attach:

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

Date of PREA PMR:

Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC? Yes No If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the protocols.

Example:

DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration:** *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

<p><i>* If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)</i></p>
<p>Types of Studies/ Study Design: <i>Example:</i> <i>Study 1: Multi-center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.</i> <i>Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.</i></p>
<p>Age group and population in which study/ies was/were performed: <i>Example:</i> <i>Study 1: patients aged X to Y years.</i> <i>Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.</i></p>
<p>Number of patients studied or power of study achieved: <i>Example:</i> <i>Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.</i> <i>Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .</i></p>
<p>Entry criteria: This section should list pertinent inclusion/exclusion criteria. <i>Example:</i> <i>Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs</i> <i>Patients had a negative pregnancy test if female.</i></p>
<p>Clinical endpoints:</p>

<p><i>Example:</i> <i>Study 1: Clinical outcome and safety were the primary endpoints.</i></p>	<p><i>Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F</i></p> <p>Statistical information (statistical analyses of the data performed): This section should list the statistical tests conducted.</p> <p><i>Example:</i> <i>Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.</i></p> <p><i>Study 2: descriptive statistical methods for AUC, C max, Tmax, CL/F and compared to adults.</i></p>
<p>Timing of assessments: <i>Example:</i> <i>Baseline, week 2, week 6, and end of treatment</i></p>	

Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.