

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205003Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

205003

NAME OF APPLICANT / NDA HOLDER

Symplimed Pharmaceuticals LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

(Prestalia)

ACTIVE INGREDIENT(S)

Perindopril arginine
Amlodipine besylate

STRENGTH(S)

Perindopril arginine/Amlodipine besylate: 3.5/2.5 mg, 7/5 mg, 14/10 mg

DOSAGE FORM

Fixed-dose combination film-coated tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

I will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number U.S. Patent No. 6,696,481	b. Issue Date of Patent 02/24/2004	c. Expiration Date of Patent 04/15/2023
d. Name of Patent Owner Les Laboratoires Servier	Address (of Patent Owner) 50 Rue Carnot	
	City/State Suresnes, France	
	ZIP Code 92150	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> No		

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Claim 5		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Prestalia is indicated for the treatment of hypertension. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

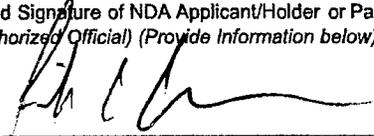
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



2/25/14

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Erik Emerson- Symplmed Pharmaceuticals, LLC

Address

5375 Medpace Way

City/State

Cincinnati, OH

ZIP Code

45227

Telephone Number

(888) 552-9769

FAX Number (if available)

E-Mail Address (if available)

emerson@symplmed.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.3.5.2 PATENT CERTIFICATION

NORVASC

PARAGRAPH II CERTIFICATION

Symplmed Pharmaceuticals LLC by this application submitted under 21 U.S.C. §355(b)(2) [Sec. 505(b)(2) of the Federal Food, Drug and Cosmetic Act, as amended] is requesting approval of PRESTALIA (perindopril arginine/amlodipine besylate).

Symplmed Pharmaceuticals LLC hereby states, on information and belief, that Pfizer is the holder of Application No. 019787 approved July 31, 1993 for Norvasc.

Symplmed Pharmaceuticals LLC hereby states, on information and belief that U.S. Patent No. 4,879,303 is listed in Approved Drug Products as covering Norvasc. This patent expired on March 25, 2007.

Symplmed Pharmaceuticals LLC hereby states, on information and belief that U.S. Patent No. 4,572,909 is listed in Approved Drug Products as covering Norvasc. This patent expired on July 31, 2006.

1.3.5.2 PATENT CERTIFICATION

ACEON

PARAGRAPH II CERTIFICATION

Symplmed Pharmaceuticals LLC by this application submitted under 21 U.S.C. §355(b)(2) [Sec. 505(b)(2) of the Federal Food, Drug and Cosmetic Act, as amended] is requesting approval of PRESTALIA (perindopril arginine/amlodipine besylate).

Symplmed Pharmaceuticals LLC hereby states, on information and belief, that Symplmed Pharmaceuticals LLC is the holder of Application No. 020184 approved December 30, 1993 for ACEON.

Symplmed Pharmaceuticals LLC hereby states, on information and belief that U.S. Patent No. 4,508,729 is listed in Approved Drug Products as covering ACEON. This patent expired on August 20, 2006.

Symplmed Pharmaceuticals LLC hereby states, on information and belief that U.S. Patent No. 5,162,362 is listed in Approved Drug Products as covering ACEON. This patent expired on November 10, 2009.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW
DRUG OR BIOLOGIC FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338

Expiration Date: December 31, 2013

See PRA Statement on page 3.

1. Date of Submission (mm/dd/yyyy)

08/18/2014

APPLICANT INFORMATION

2. Name of Applicant

Symplmed Pharmaceuticals, LLC

3. Telephone Number (Include country code if applicable and area code)

(888) 552-9769 ext 101

4. Facsimile (FAX) Number (Include country

code if applicable and area code) (541) 647-1676

5. Applicant Address

Address 1 (Street address, P.O. box, company name c/o)

5375 Medpace Way

Address 2 (Apartment, suite, unit, building, floor, etc.)

City

Cincinnati

State/Province/Region

OH

Country

United States

ZIP or Postal Code

45227-1543

Email Address

emerson@symplmed.com

U.S. License Number if previously issued

6. Authorized U.S. Agent (Required for non-U.S. applicants)

Authorized U.S. Agent Name

Address 1 (Street address, P.O. box, company name c/o)

Address 2 (Apartment, suite, unit, building, floor, etc.)

City

State

ZIP Code

Telephone Number (Include area code)

FAX Number (Include area code)

Email Address

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number

205003

8. Supplement Number (If applicable)

0015

9. Established Name (e.g., proper name, USP/USAN name)

Perindopril arginine/amlodipine besylate

10. Proprietary Name (Trade Name) (If any)

Pending approval: Prestalia

11. Chemical/Biochemical/Blood Product Name (If any)

PERa: L-arginine (2S,3aS,7aS)-1- [(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino] propanoyl] octahydro-1H-indole-2-carboxylate AML: 3-ethyl-5-m

12. Dosage Form

Tablet

13. Strengths

3.5/2.5 mg, 7/5 mg, 14/10 mg

14. Route of Administration

oral

15. Proposed Indication for Use

hypertension

Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes NoDoes this product have an FDA
Orphan Designation for this
indication? Yes NoIf yes, provide the Orphan
Designation number for this
indication: Contin.
Page for
#15

APPLICATION INFORMATION

16. Application Type

(Select one)

New Drug Application (NDA)

Biologics License Application (BLA)

Abbreviated New Drug Application (ANDA)

17. If an NDA, identify the type

 505 (b)(1) 505 (b)(2)

18. If a BLA, identify the type

 351 (a) 351 (k)

19. If a 351(k), identify the biological reference product that is the basis for the submission.

Name of Biologic: _____

Holder of Licensed Application: _____

20. If an ANDA, or 505(b)(2), identify the listed drug product that is the basis for the submission.

Name of Drug: ACEON and NORVASC

Application Number of Relied Upon Product: #020184 and #019787

Indicate Patent Certification(s):

 P1 P2 P3 P4 Section viii - MOU Statement of no relevant patents

21. Submission (Select one)

 Original Labeling Supplement CMC Supplement Efficacy Supplement Annual Report Product Correspondence REMS Supplement Postmarketing Requirements or Commitments Periodic Safety Report Other (Specify): Response to Information Requests dated 11 and 15 August 2014

22. Submission Sub-Type	<input type="checkbox"/> Presubmission	<input checked="" type="checkbox"/> Amendment	23. If a supplement, identify the appropriate category.	<input type="checkbox"/> CBE	<input type="checkbox"/> Prior Approval (PA)
	<input type="checkbox"/> Initial Submission	<input type="checkbox"/> Resubmission		<input type="checkbox"/> CBE-30	

24. Does this submission contain *only* pediatric data? Yes No

25. Reasons for Submission
Response to Information Requests dated 11 and 15 August 2014

26. Proposed Marketing Status (Select one) Prescription Product (Rx) Over-The-Counter Product (OTC)

27. This application is (Select one) Paper Paper and Electronic Electronic

28. Number of Volumes Submitted

29. Establishment Information (Full establishment information should be provided in the body of the application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, registration number (FEI), MF number, Establishment DUNS number, and manufacturing steps and/or type of testing (e.g., final dosage form, stability testing, container closure) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Establishment Name Patheon Pharmaceuticals, Inc, a Subsidiary of Patheon, Inc.		Registration (FEI) Number (b) (4)	
Address 1 (Street address, P.O. box, company name c/o) 2110 East Galbraith Road		MF Number	
Address 2 (Apartment, suite, unit, building, floor, etc.)			
City Cincinnati	State/Province/Region OH		
Country United States	ZIP or Postal Code 45237-1625		
Is the establishment new to the application?		What is the status of the establishment?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		<input type="checkbox"/> Pending <input checked="" type="checkbox"/> Active <input type="checkbox"/> Inactive <input type="checkbox"/> Withdrawn	

Establishment Contact Information

Name of Contact for the Establishment Mr. David Leuck, Director of Quality Operations	Telephone Number (Include area code) (513) 948-6358
Address 1 (Street address, P.O. box, company name c/o) 2110 East Galbraith Road	FAX Number (Include area code) (513) 948-7393
Address 2 (Apartment, suite, unit, building, floor, etc.)	Email Address David.Leuck@patheon.com
City Cincinnati	State OH
ZIP or Postal Code 45237-1625	

Manufacturing Steps and/or Type of Testing XOMA 985 Tablets Manufacturing, Packaging, and Quality Control Release and Stability Testing	Is the site ready for inspection? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If No, when will site be ready? (mm/dd/yyyy)
Continuation Page for #29	

30. Cross References (List related BLAs, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, MAFs, and DMFs referenced in the current application.)

IND:108.233

(b) (4) **Contin. Page for #30**

31. This application contains the following items (Select all that apply)

<input type="checkbox"/> 1. Index	<input type="checkbox"/> 2. Labeling (Select one): <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	<input type="checkbox"/> 3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/> 4. Chemistry Section	<input type="checkbox"/> A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
	<input type="checkbox"/> B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	<input type="checkbox"/> C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/> 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	<input type="checkbox"/> 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input type="checkbox"/> 7. Clinical microbiology section (e.g., 21 CFR 314.50(d)(4))	<input type="checkbox"/> 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	

Item 31 continued on page 3

31. This application contains the following items (Continued; select all that apply)

<input type="checkbox"/> 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	<input type="checkbox"/> 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/> 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	<input type="checkbox"/> 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/> 13. Patent information on any patent that claims the drug/biologic (21 U.S.C. 355(b) or (c))	<input checked="" type="checkbox"/> 14. A patent certification with respect to any patent that claims the drug/biologic (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/> 15. Establishment description (21 CFR Part 600, if applicable)	<input type="checkbox"/> 16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/> 17. Field copy certification (21 CFR 314.50 (l)(3))	<input type="checkbox"/> 18. User Fee Cover Sheet (PDUFA Form FDA 3397, GDUFA Form FDA 3794, BsUFA Form FDA 3792, or MDUFMA Form FDA 3601)
<input type="checkbox"/> 19. Financial Disclosure Information (21 CFR Part 54)	
<input checked="" type="checkbox"/> 20. Other (Specify): Response to Information Requests dated 11 and 15 August 2014	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

32. Typed Name and Title of Applicant's Responsible Official Erik Emerson, President and CEO	33. Date (mm/dd/yyyy) 08/18/2014
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34. Telephone Number (Include country code if applicable and area code) (888) 552-9769 ext 101	35. FAX Number (Include country code if applicable and area code) (541) 647-1676	36. Email Address emerson@symplmed.com
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37. Address of Applicant's Responsible Official			
Address 1 (Street address, P.O. box, company name c/o) 5375 Medpace Way			
Address 2 (Apartment, suite, unit, building, floor, etc.)			
City Cincinnati		State/Province/Region OH	
Country United States		ZIP or Postal Code 45227-1543	

38. Signature of Applicant's Responsible Official or Other Authorized Official Erik Emerson <small>Digitally signed by Erik Emerson DN: cn=Erik Emerson, o=Symplmed Pharmaceuticals, ou=CEO, email=emerson@symplmed.com, c=US Date: 2014.08.18 08:10:44 -07'00'</small>	Sign	39. Countersignature of Authorized U.S. Agent	Sign
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The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 24 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.

FIRST CONTINUATION PAGE FOR ITEM 29 – Establishment Information		Provide information for additional establishments below, as needed.
Establishment Name (b) (4)		
Address 1 (Street address, P.O. box, company name c/o) (b) (4)		Registration (FEI) Number (b) (4)
Address 2 (Apartment, suite, unit, building, floor, etc.)		MF Number (b) (4)
City Budapest	State/Province/Region	Establishment DUNS Number
Country Hungary	ZIP or Postal Code H1106	
Is the establishment new to the application? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		What is the status of the establishment? <input type="checkbox"/> Pending <input checked="" type="checkbox"/> Active <input type="checkbox"/> Inactive <input type="checkbox"/> Withdrawn
Establishment Contact Information		
Name of Contact for the Establishment (b) (4)		Telephone Number (Include area code) (b) (4)
Address 1 (Street address, P.O. box, company name c/o) (b) (4)		FAX Number (Include area code) (b) (4)
Address 2 (Apartment, suite, unit, building, floor, etc.)		Email Address (b) (4)
City Budapest	State Hungary	
ZIP or Postal Code (b) (4)		
Manufacturing Steps and/or Type of Testing Amlodipine Besylate - Manufacturing, Testing, and Release		Is the site ready for inspection? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If No, when will site be ready? (mm/dd/yyyy) _____
Establishment Name Cadila Pharmaceuticals Ltd.		
Address 1 (Street address, P.O. box, company name c/o) (b) (4)		Registration (FEI) Number (b) (4)
Address 2 (Apartment, suite, unit, building, floor, etc.) (b) (4)		MF Number (b) (4)
City (b) (4)	State/Province/Region	Establishment DUNS Number (b) (4)
Country (b) (4)	ZIP or Postal Code (b) (4)	
Is the establishment new to the application? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		What is the status of the establishment? <input type="checkbox"/> Pending <input checked="" type="checkbox"/> Active <input type="checkbox"/> Inactive <input type="checkbox"/> Withdrawn
Establishment Contact Information		
Name of Contact for the Establishment Mr. Ranga Raju Kakarlapudi, Vice President – Quality		Telephone Number (Include area code) +91-2646-252626, 251519
Address 1 (Street address, P.O. box, company name c/o) 294, G.I.D.C Industrial Estate		FAX Number (Include area code) +91-2646-250051
Address 2 (Apartment, suite, unit, building, floor, etc.) Ankleshwar – 393 002		Email Address k.rangaraju@cadilapharma.co.in
City Gujarat	State India	
ZIP or Postal Code 00039-3002		
Manufacturing Steps and/or Type of Testing Amlodipine Phthaloyl Intermediate - Manufacturing, Testing, and Release		Is the site ready for inspection? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If No, when will site be ready? (mm/dd/yyyy) _____
Add Second Continuation Page for #29		

SECOND CONTINUATION PAGE FOR ITEM 29 – Establishment Information		<i>Provide information for additional establishments below, as needed.</i>
Establishment Name (b) (4)		Registration (FEI) Number (b) (4)
Address 1 (Street address, P.O. box, company name c/o) (b) (4)		MF Number (b) (4)
Address 2 (Apartment, suite, unit, building, floor, etc.)		Establishment DUNS Number (b) (4)
City Bolbec	State/Province/Region	
Country (b) (4)	ZIP or Postal Code (b) (4)	
Is the establishment new to the application? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		What is the status of the establishment? <input type="checkbox"/> Pending <input checked="" type="checkbox"/> Active <input type="checkbox"/> Inactive <input type="checkbox"/> Withdrawn
Establishment Contact Information		
Name of Contact for the Establishment (b) (4)		Telephone Number (Include area code) (b) (4)
Address 1 (Street address, P.O. box, company name c/o) (b) (4)		FAX Number (Include area code) (b) (4)
Address 2 (Apartment, suite, unit, building, floor, etc.)		Email Address (b) (4)
City (b) (4)	State (b) (4)	
ZIP or Postal Code (b) (4)		
Manufacturing Steps and/or Type of Testing Perindopril Arginine - Manufacturing, Testing, and Release		Is the site ready for inspection? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If No, when will site be ready? (mm/dd/yyyy) _____

Establishment Name Symplmed Pharmaceuticals, LLC		Registration (FEI) Number
Address 1 (Street address, P.O. box, company name c/o) 5375 Medpace Way		MF Number
Address 2 (Apartment, suite, unit, building, floor, etc.)		Establishment DUNS Number 079198402
City Cincinnati	State/Province/Region OH	
Country United States	ZIP or Postal Code 45227-1543	
Is the establishment new to the application? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		What is the status of the establishment? <input type="checkbox"/> Pending <input checked="" type="checkbox"/> Active <input type="checkbox"/> Inactive <input type="checkbox"/> Withdrawn
Establishment Contact Information		
Name of Contact for the Establishment Mr. Erik Emerson, President and CEO		Telephone Number (Include area code) (888) 552-9769 ext 101
Address 1 (Street address, P.O. box, company name c/o) 5375 Medpace Way		FAX Number (Include area code) (541) 647-1676
Address 2 (Apartment, suite, unit, building, floor, etc.)		Email Address emerson@symplmed.com
City Cincinnati	State OH	
ZIP or Postal Code 45227-1543		
Manufacturing Steps and/or Type of Testing XOMA 985 Tablets Release		Is the site ready for inspection? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If No, when will site be ready? (mm/dd/yyyy) _____
Add Third Continuation Page for #29		

1.3.5.2 PATENT CERTIFICATION

PARAGRAPH I CERTIFICATION

Symplmed Pharmaceuticals LLC by this application submitted under 21 U.S.C. §355(b)(2) [Sec. 505(b)(2) of the Federal Food, Drug and Cosmetic Act, as amended] is requesting approval of PRESTALIA (perindopril arginine/amlodipine besylate).

Symplmed Pharmaceuticals LLC hereby states, on information and belief, that there are no patents that claim the drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drugs.

EXCLUSIVITY SUMMARY

NDA # 205003

SUPPL #

HFD #

Trade Name Prestalia

Generic Name Perindopril arginine and Amlodipine

Applicant Name Symplmed Pharmaceuticals LLC

Approval Date, If Known 1-21-15

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

List of approved perindopril and amlodipine approved products with NDA#s.

NDA# NDA 19787 Norvasc

NDA# NDA 20184 Aceon

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES X NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20184

NDA# 19787

NDA#

Note that NDA 20184, Aceon, contains Perindopril erbumine. Prestalia contains Perindopril arginine, which has not been approved in the US. Both Perindopril and Amlodipine have been approved in combination products, but not in the same combination product.

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES X NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES X NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO X

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES X NO

If yes, explain:

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.

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

YES NO X

YES NO X

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #1

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

YES NO X

YES NO X

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 (X985400) Phase 3

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 108233 YES X ! NO
! Explain:

Name of person completing form: Wayne Amchin

Title: Senior CSO

Date: January 19, 2015

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.

Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

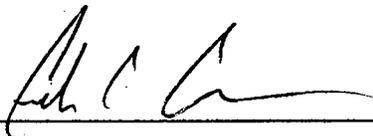
/s/

WAYNE S AMCHIN
01/21/2015

NORMAN L STOCKBRIDGE
01/21/2015

1.3.3 DEBARMENT CERTIFICATION

Symplmed Pharmaceuticals, LLC 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.



Erik Emerson
President and Chief Executive Officer
Symplmed Pharmaceuticals, LLC

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

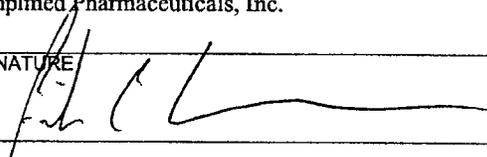
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please see attached lists	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Erik Emerson	TITLE President & CEO
FIRM/ORGANIZATION Symplmed Pharmaceuticals, Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) 02/25/2014

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
PRAStaff@fda.hhs.gov

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CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

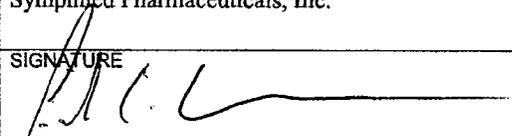
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Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Erik Emerson	TITLE President & CEO
FIRM/ORGANIZATION Symplmed Pharmaceuticals, Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) 02/25/2014

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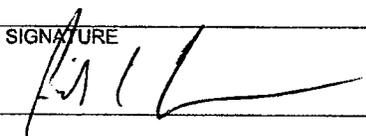
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Erik Emerson	TITLE President & CEO
FIRM/ORGANIZATION Symplmed Pharmaceuticals, Inc.	
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Department of Health and Human Services
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Office of Chief Information Officer
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"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

1.3.4 FINANCIAL CERTIFICATION AND DISCLOSURE

The investigators listed below did not enter into any financial arrangements with Symplmed Pharmaceuticals, LLC (Symplmed) whereby the value of compensation to the investigators could be affected by the outcome of the studies. The following studies are included:

- **Table 1: X985401 Investigators**
- **Table 2: PKH-05985-001 Investigators**
- **Table 3: PKH-05985-009 Investigators**
- **Table 4: CL2-05985-005 Investigators**
- **Table 5: X985400 Investigators**

Investigators, sub-investigators (SI) if applicable, and site addresses are listed for each study. For studies with multiple sites, the corresponding site numbers are listed for investigator.

Studies X985401 and X985400 were conducted by the applicant and correspond to Box 1 on Form FDA 3454. Studies PKH-05985-001, PKH-05985-009, and CL2-05985-005 were conducted by a party other than the applicant and correspond to Box 2 on Form FDA 3454.

For the CL2-05985-005 study, a list of investigators who could not be located to sign the financial disclosure form after due diligence can be found in **Table 6**. This information corresponds to Box 3 on Form FDA 3454.

Table 1: X985401 Investigators

Investigators(s)	Address
BIERNAT, Lukasz (b) (4)	5375 Medpace Way Cincinnati, OH 45227

Table 2: PKH-05985-001 Investigators

Investigator	Address
DONAZZOLO, Yves	1 rue des Essarts 38610 GIERES, France

Table 3: PKH-05985-009 Investigators

Investigator	Address
ALBALADEJO, Magi	Doctor Aiguader, 88 08003 BARCELONA, Spain

Table 4: CL2-05985-005 Investigators

Site #	Investigator(s)	Address
0100	CONSTANTIN, Gérard	16 rue Emile Martin 18000 BOURGES, FRANCE
0101	BEAUDOIN, Jacques	26, route de Vierzon 18120 LURY SUR ARNON, FRANCE
0102	BOICHE, Paola	121 av. du Général de Gaulle 18000 BOURGES, FRANCE
0105	PIPET, Linh	1, rue du Dr. J-C SO URNIA 18000 BOURGES, FRANCE
0106	SUNDA, Mavungu	Centre Medical 32 rue Louis Beydts 33310 LORMONT, FRANCE
0200	SPIILTHOOREN, Francois	16 rue de la Rangearderie 17260 VILLARS EN PONS, FRANCE
0202	EDET, Dominique	30 rue de Bayeux 14740 BRETTEVILLE L'ORGUEILLEUSE, FRANCE
0203	MABIRE, Pascal	126 route d'Harcourt 14123 FLEURY SUR ORNE, FRANCE
0204	MOREL, Herve	1 rue de Bayeux 14250 TILLY SUR SEULLES, FRANCE
0300	MONGIN, Gérald	82 avenue d'Assas 34000 MONTPELLIER, FRANCE
0301	ALEA, Jean-Roch	82 avenue Assas 34000 MONTPELLIER, FRANCE
0303	LOGNOS-FOLCO, Beatrice	rue de Clairdouy 34680 ST GEORGES D'ORQUES, FRANCE
0304	MARTOCQ, Grégoire	13 rue du Dr Malabouche 34660 CURNONTERRAL, FRANCE
0306	SARAÏS, Oliver	3, rue de la mairie 34110 VIC LA GARDIOLE, FRANCE
0307	TEISSEIRE, Jean-Paul	Villa 54 Residence le Village 14 bis avenue Jean Jaurès 34170 CASTELNAU LE LEZ, FRANCE
0400	BOYE, Alain	63 rue de la Bottière 44300 NANTES, FRANCE
0402	COISNE, Eric	27 rue de Brocéliande 35137 BEDEE, FRANCE
0403	COLAS, Anne-Elisabeth	4 rue du Champ Dolent 35700 RENNES, FRANCE
0406	DELARUE, Jean-Marie	3 place de la Gare 35490 SENS DE BRETAGNE, FRANCE
0408	DUREL, Gaël	1 rue de l'Ecotay 35190 TINTENIAC, FRANCE

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
0411	LEMARIE, Bruno	8 rue des Nouettes 35410 CHATEAUGIRON, FRANCE
0412	LOCHET, Eric	1 rue Charles Robert 35120 DOL DE BRETAGNE, FRANCE
0413	LOCHET-GOARANT, Sylvie	3 rue de la cour Gougeon 35111 LA FRESNAIS, FRANCE
0414	RANGE, Patrick	C. Cial la Bellangerais rue du Morbihan 35700 RENNES, FRANCE
0415	ZIMMERMANN, Daniel	Chemin des Diligences 35680 LOUVIGNE DE BAIS, FRANCE
0500	CAMPAGNE, Alain	15 rue du Dr. Jacques Marie Rougé 37000 TOURS, FRANCE
0502	BIQUET, Dominique	30 avenue du Gl de Gaulle 37550 SAINT AVERTIN, FRANCE
0503	CAMPER, Emmanuel	17 rue Manuel 37400 AMBOISE, FRANCE
0504	HUMBERT, Thierry	21 Rue Chatonnay 37510 SAVONNIERES, FRANCE
0506	MERCIER, Pierre	1 et 3 rue Maryse Bastié 37000 TOURS, FRANCE
0507	PRADERE, Henri	30 av. du Général De Gaulle 37550 SAINT AVERTIN, FRANCE
0508	LEPRINCE, Patrick	1 et 3 rue Maryse Bastié 37000 TOURS, FRANCE
0600	EL SAWY, Alain	1 rue Franz Schubert 38400 St MARTIN D'HERES, FRANCE
0601	AZZOPARDI, Yves	15 chemin Joseph Brun 38100 GRENOBLE, FRANCE
0603	CHASSERY, Brigitte	3 place Louis Maisonnat 38610 FONTAINE, FRANCE
0605	ECOCHARD CIRICA, Nadine	20 avenue Paul Eluard 38400 St. MARTIN D'HERES, FRANCE
0607	YEM, S.A.	35 Bd Marechal Foch 38000 GRENOBLE, FRANCE
0608	DE VERCOURT, Guillaume	1 rue Franz Schubert 38400 SAINT MARTIN D'HERES, FRANCE
0609	PETERS, Francois	22 Avenue Leon Blum 38000 GRENOBLE, FRANCE
0700	PINEAU-VALENCIENNE, Dominique	63 rue de la Bottière 44300 NANTES, FRANCE
0701	ALGABA, Pedro	4 bld de Strasbourg 44390 NORT SUR ERDRE, FRANCE

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
0702	BARAT, Veronique	1 impasse des Loriots 44115 HAUTE GOULAIN, FRANCE
0703	COUFFIN, Yvon	17 rue de l' Erdre 44240 LA CHAPELLE SUR ERDRE, FRANCE
0704	De COLLART, Gwendal	6 rue Filée 44140 AIGREFEUILLE SUR MAINE, FRANCE
0705	EOCHE, Roger	101 bld de Doulon 44300 NANTES, FRANCE
0706	FAWAZ, Abbas	2 impasse Dublin 44800 SAINT HERBLAIN, FRANCE
0707	FOURNIER, Henri	25, rue de la Martelière 44230 ST SEBASTIEN sur LOIRE, FRANCE
0708	GODDE, Pascal	6 rue de la Gaudinai 44110 ST AUBIN des CHATEAUX, FRANCE
0713	MULLER, Patrick	14 Rue De L Estuaire 44560 CORSEPT, FRANCE
0714	MUSSAT, Patrick	9 pl. Sainte Anne 44640 VUE, FRANCE
0715	PIQUET, Patrick	76 rue des Orrmeaux 44521 OUDON, FRANCE
0716	THIBAUT, Richard	3 rue Jean-Baptiste Auffray 44360 ST ETIENNE DE MONTLUC, FRANCE
0717	TOURNEMINE, Nicolas	30 rue de la Vallee 44880 SAUTRON, FRANCE
0800	MARTY, Jacques	25 rue Valentin Des Ormeaux 49610 MURS ERIGNE, FRANCE
0802	AMBLARD, Patrick	rue du Petit Montrevault 49110 ST PIERRE MONTLIMART, FRANCE
0803	BAERT, Michel	38 avenue de Leuze 86200 LOUDUN, FRANCE
0805	BEDOUET, Regis	25 avenue de Nantes 49300 CHOLET, FRANCE
0808	BOUCHER, Loïc	25 rue du Stade 49610 MURS ERIGNE, FRANCE
0809	BUFFARD, Bruno	29 rue du Stade 49390 PARCAY LES PINS, FRANCE
0810	CHARRIER, Bruno	8 Chemin des Vendéens 49510 LA JUBAUDIERE, FRANCE
0812	COULIS, Thierry	11 av. de la Chesnaie 49130 LES PONTS DE CE, FRANCE
0815	DE SAUVEBOEUF, Francois	1 rue Pasteur 49122 LE MAY SUR EVRE, FRANCE

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
0816	FALIGOT, Serge	14 Rue Faidherbe 49300 CHOLET, FRANCE
0817	FOUBERT, Oliver	8, rue Seguin 53200 CHÂTEAU GONTIER BAZOUGES, FRANCE
0818	GACHET, Luc	7 route Gagnebert 49610 JUIGNE SUR LOIRE, FRANCE
0819	GAUGAIN, Jean-Bernard	59 bld Joseph Bédier 49000 ANGERS, FRANCE
0820	HENRI, Philippe	1, avenue des Erables 49125 TIERCE, FRANCE
0822	JEAN, Michel	47 rue Racine 49169 LONGUE JUMELLES, FRANCE
0827	MILLIOT, Alain	11 route de la forêt 49070 ST JEAN DE LINIERES, FRANCE
0829	OSHO, Yves	106 Place du Gué des Joncs 85600 ST GEORGES DE MONTAIGU, FRANCE
0831	PITHON, Francois	18 rue Martin Luther King 49000 ANGERS, FRANCE
0832	SCHAUPP, Thierry	4 rue Beaurepaire 49310 VIHIERES, FRANCE
0833	SIMON, Jean-Paul	3 rue du Port Martin 49800 BRAIN SUR L'AUTHION, FRANCE
0834	SOULARD, Jean-Pierre	25 avenue de Nantes 49300 CHOLET, FRANCE
0835	TIROUFLET, Daniel	24 rue Julien Daillière 49140 BAUNE, FRANCE
0900	RICHTER, Dominique	25 Rue du Point du Jour 54800 JARNY, FRANCE
0905	MAURIERE, Serge	26 rue President Wilson 57130 ARS SUR MOSELLE, FRANCE
0906	MOULLA, Mustapha	47 boulevard Ney 54700 PONT A MOUSSON, FRANCE
0911	JACQUES, Jean-Luc	8 Rue Georges Thiébaux 54800 MARS LA TOUR, FRANCE
1001	BERMOND, Yves	10 rue Jacques Thézac 56000 VANNES, FRANCE
1003	EVENO, Marie-Pierre	41 rue St Yves 56390 GRAND CHAMP, FRANCE
1004	LE GUERROUE, Alain	4 rue André Chamson 56000 VANNES, FRANCE
1005	LEMOINE, Christophe	15 place de la république 56000 VANNES, FRANCE

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
1007	MARZIN, Yves	Rue Pasteur 56400 LE BONO, FRANCE
1100	LEJAY, Dominique	200 rue Jean Jaures 59690 VIEUX CONDE, FRANCE
1101	DELSART, Dominique	24 bis, rue de la Motte 59235 BERSEE, FRANCE
1102	GRASSART, Emmanuel	1 Résidence Marcel Paul 59138 BACHANT, FRANCE
1103	MARLIER, Mathieu	1 rue Volta 59130 LAMBERSART, FRANCE
1108	SPECHT, Lionel	1 rue Volta 59130 LAMBERSART, FRANCE
1109	VOGEL, Jacques	61 rue amiral Courbet 59170 CROIX, FRANCE
1110	HERENT, Marc	117 ter rue Jean Jaurès 59410 ANZIN, FRANCE
1200	FAUGAS, Gilles	12 rue de la belle Gabrielle 72000 LE MANS, FRANCE
1201	CRAPPIER, Jean-Jacques	16 pl. de l'Eperon 72000 LE MANS, FRANCE
1202	JOLY, Frédéric	4 Avenue d'Haouza 72100 LE MANS, FRANCE
1203	JOUSSET, Olivier	3 boulevard Matthews 72230 MONCE EN BELIN, FRANCE
1204	PAILLARD, Guy-Marc	3 boulevard Matthews 72230 MONCE EN BELIN, FRANCE
1205	VANPRAET, Jean-Jacques	7 rue de la Vienne 72190 COULAINES, FRANCE
1300	DE SAINTE LORETTE, Eric	6 avenue de la Motte Piquet 75007 PARIS, FRANCE
1301	AUDOUY, Patrick	79 rue Boissiere 75116 PARIS XVI, FRANCE
1302	BEAUNIER, Philippe	88 rue de Sèvres 75007 PARIS, FRANCE
1303	CHABAUD, Eric	6 Grande Rue 91840 SOISY SUR ECOLE, FRANCE
1304	DELBECQ, Daniel	40 rue du Faubourg Montmartre 75009 PARIS, FRANCE
1305	JUDE, Nicolas	19 boulevard Morland 75004 PARIS IV, FRANCE
1306	MOUCHET, Jean-Claude	10 rue de la République 92190 MEUDON, FRANCE

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
1308	SEBBAH, Andre	31 avenue Felix Faure 75015 PARIS XV, FRANCE
1400	BEIGNOT DEVALMONT, Philippe	102 rue Meridienne 76100 ROUEN, FRANCE
1401	BLOT, Etienne	45 bld de l'Yser 76000 ROUEN, FRANCE
1402	GONTHARET, Bernard	35 av. du President Kennedy 76120 LE GRAND QUEVILLY, FRANCE
1405	SPIESS, Hans-Wolfgang	102 rue Meridienne 76100 ROUEN, FRANCE
1406	BOULENGE, Jerome	102 rue Meridienne 76100 ROUEN, FRANCE
1407	DURET ROLLAND, Mathilde	102 rue Meridienne 76100 ROUEN, FRANCE
1501	AUPY, Jean-Marc	15 place du Champ de Foire 79220 CHAMPDENIERS, FRANCE
1502	DUPONT, Serve	24 rue de la Poste 79000 NIORT-SOUCHE, FRANCE
1503	LHOUMEAU, Patrick	17 rue de Tilleuls 79160 VILLERS EN PLAINE, FRANCE
1504	PINSEMBERT, Daniel	40 bld Anatole France 79200 PARTHENAY, FRANCE
1506	BENAYOUNE, Serge	9 rue de la Cure 79160 FENIOUX, FRANCE
1507	TILLY, Catherine	277 avenue de la Rochelle 79000 NIORT, FRANCE
1602	DUMOND, Philippe	30 av. Gallieni Les résidences du Port 83110 SANARY SUR MER, FRANCE
1604	RIPOLL, Marc	112 avenue du XVeme Corps 83200 TOULON, FRANCE
1700	LATTE, Thierry	15 rue Jean Yole 85150 ST JULIEN DES LANDES, FRANCE
1701	GRELLIER, Patrick	31, rue de la La Maladrie 85210 SAINTE HERMINE, FRANCE
1703	PIFFETEAU-GASTON, Isabelle	11 rue de Nantes 85190 AIZENAY, FRANCE
1704	VOISIN, Thierry	31 rue de la Maladrie 85210 SAINTE HERMINE, FRANCE
1802	CORDIER, Francois	28 route Merlande 33350 SAINTE TERRE, FRANCE
1804	DANTIN, Guillaume	8 Av. Georges Clémenceau 33140 VILLENAVE D'ORNON, FRANCE

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
1805	DELACHIENNE, André	27 bis av. de la Belle Etoile 33270 BOULIAC, FRANCE
1806	DUROUX, Gérard	1 rue Joffre 33260 LA TESTE, FRANCE
1808	GARRIGUE, Luc	17 rue de la Charmille 33112 ST LAURENT DU MEDOC, FRANCE
1811	HOCQUELET, Jean-Francois	33 rue Jean Jaurès 33530 BASSENS, FRANCE
1812	KRESSMANN, Emmanuel	Centre Commercial Chamboparc 33140 VILLENAVE D'ORNON, FRANCE
1815	MAGDELEINE, Christophe	112 av Montesquieu 33160 ST MEDARD EN JALLE, FRANCE
1820	SIBILLE, Patrick	2 Ter rue du Stade 33480 AVENSAN, FRANCE
1822	VEAUX, Philippe	53, boulevard du Général Leclerc 33120 ARCACHON, FRANCE
3000	LAUCEVICIUS, Aleksandras (b) (4)	Vilnius University Hospital Santariskiu Klinikos (VUH SK) Santariskiu str. 2 Vilnius LT-2021, LITHUANIA
3002	BERUKSTIS, Egidijus (b) (4)	Private Medical Clinic "COR SANUM" Pamenkalnio str. 25-2 Vilnius, LT-01113, LITHUANIA
3003	JANKAUSKIENE, Laima (b) (4)	Kaunas 2nd clinical hospital Josvainiu str. 2 Kaunas, LT-47144, LITHUANIA
3004	JARASUNIENE, Dalia (b) (4)	Klaipeda Seamen's hospital Cardiology Department Liepojos str. 45 Klaipeda, LT-92288, LITHUANIA
3005	KIBARSKIS, Aleksandras (b) (4)	Private Cardiologic Clinic JSC "Heart House" M.Paco str. 7/2-1 Vilnius, LT-10309, LITHUANIA
3006	KAVOLIUNIENE, Ausra (b) (4)	Kaunas Medical University Hospital Clinic of Cardiology 2nd Department of Cardiology Eivenių str. 2 Kaunas, LT-5009, LITHUANIA

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
3007	PETRULIONIENE, Zaneta (b) (4)	Center of Cardiology and Angiology Vilnius University Hospital Santariskiu Clinics Santariskiu 2 08661 VILNIUS, LITHUANIA
3008	ZABIELA, Petras (b) (4)	Kaunas Regional Hospital Department of Cardiology Hipodromo str.13 Kaunas, LT-45130, LITHUANIA
4000	MINTALE, Iveta (b) (4)	Latvian Centre of Cardiology P. Stradins Clinical University Hospital 13 Pilsonu street Riga LV 1002, LATVIA
4001	ABELE, Santa (b) (4)	Santas Abeles Private practice Zemgales pr. 15 Jelgava, LV-3001, LATVIA
4002	ROZKOVA, Nadezda (b) (4)	Clinical Hospital Gailizers Hipokrata str 2 Riga, LV-1038, LATVIA
4003	BUDREVICA, Solveiga (b) (4)	Health Centre 117 Kr.Barona str Riga, LV-1012, LATVIA
4004	DORMIDONTOVA, Galina (b) (4)	JSC "Meda-D", Outpatient Clinic Vienibas str. 8-38 Daugavpils, LV-5403, LATVIA
4005	SAULITE-KANDEVICA, Daina (b) (4)	D.Saulites-Kandevicas private practice 20/24 Aldaru str Liepaja, LV-3400, LATVIA
5000	LITVIN, Alexander (b) (4)	Federal State Institution Russian Cardiology research and production complex of Federal Agency of High Technology Medical Aid, Department of System hypertension 3rd Cherepkovskaya str, 15A 121552 Moscow
5001	AGEEV, Fails (b) (4)	Federal State Institution Russian Cardiology research and production complex of Federal Agency of High Technology Medical Aid, Research - Dispensary department, 3rd Cherepkovskaya str, 15A 121552 Moscow, RUSSIA

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
5002	ARUTYUNOV, Grigoriy (b) (4)	City Clinical Hospital № 4 Chair of therapy of Russian State Medical University, Pavlovskaya str, 25 113093 Moscow, RUSSIA
5003	GRATSIANSKY, Nikolay (b) (4)	Federal State Institution Scientific Research Institute of Cardiology of Physico- Chemical Medicine of Roszdrav 2 Gosdpitalnaja sq 111020 Moscow, RUSSIA
5004	KARPOV, Yuri (b) (4)	Federal State Institution Russian Cardiology research and production complex of Federal Agency of High Technology Medical Aid, Angiology Department 3rd Cherepkovskaya str, 15A 121552 Moscow, RUSSIA
5005	KOBALAVA, Zhanna (b) (4)	Center for Study of new Medicines and Diagnostic Preparation of Russian State People Friendship University, based on City Clinical Hospital #64 61, Vavilova str 117292, Moscow, RUSSIA
5006	SHPAGINA, Lyubov (b) (4)	Municipal Institution of Healthcare "City Clinical Hospital #2" Polzunova str., 21 630051, Novosibirsk , RUSSIA
5007	LOPATIN, Yuriy (b) (4)	Volgograd Regional Cardiology Center Gornaya Poliana, 106, Universitetsky prospect 400008, Volgograd, RUSSIA
5008	MARTSEVICH, Sergey (b) (4)	Federal State Institution National Research Center for Preventive Medicine of Federal Agency of High Technology Medical Aid 10, Petroverigski lane 101990, Moscow, RUSSIA
5009	MOYSEEV, Valentin (b) (4)	Russian Peoples Frenship University 61, Vavilova str 117292, Moscow, RUSSIA

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
5010	MORDOVIN, Victor (b) (4)	Tomsk research Institute of Cardiology 111a, Kievskaya str 634012, Tomsk, RUSSIA
5011	NEDOGODA, Sergey	Volgograd Medical Academy Tsiolkovskogo str. 1, 400001, Volgograd, RUSSIA
5012	PEREPECH, Nikita (b) (4)	St. Petersburg City Hospital N 31 Chair of cardiology of I. Mechnikov St-Peters.State.Med.Acad Dinamo av. 3 197110 St. Petersburg, RUSSIA
5013	SCHERENKOV, Alexander (b) (4)	Medical Exercises Dispensary 15, Novocherkassky pr 195112, St. Peterburg, RUSSIA
5014	SCHLYAHTO, Evgeniy (b) (4)	I.P.Pavlov State Medical University, Federal State Institution "Almazov Federal Heart, blood and endocrinology centre of Federal Agency of High Technology Medical Aid Parhomenko, 15 194156 St. Petersburg, RUSSIA
5015	SCHVARTS, Yury (b) (4)	Saratov State Medical University, Clinical Hospital #3 137, Bolshaya Sadovaya str 410054, Saratov, RUSSIA
5016	SIMANENKOV, Vladimir (b) (4)	St.Peterburg Medical Academia Postgraduate Education, City Hospital #26 2, Kostiushko str 196247, St. Peterburg, RUSSIA
5017	TERESCHENKO, Sergey (b) (4)	Federal State Institution of Moscow City Clinical Hospital #68 4 Shkuleva str 109263 Moscow, RUSSIA
5018	VASUYK Yuriv (b) (4)	City Clinical Hospital #33 Chair of Hospital Therapy #1, Moscow St.Medico-Stomatological University Strominka str. 7, build 11 107014 Moscow, RUSSIA

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
5019	YAKUSEVICH, Vladimir (b) (4)	Municipal Health Care Institution Clinical Hospital n.a. N.V. Solovyov 11, Zagorodniy sad 150014, Yaroslavl, RUSSIA
6000	SIRENKO, Yuriy (b) (4)	Straszhesko Institute of Cardiology AMS of Ukraine 5 Narodnogo Opolchenia str Kyiv, 03151, UKRAINE
6001	BAZYLEVYCH, Andriy (b) (4)	Lviv City Hospital #5, 22 Konovaltca str Lviv , 79013, UKRAINE
6002	GOLOBORODKO, Alla (b) (4)	Odessa Regional Clinical Hospital 26 Ak.Zabolotnogo Str Odessa, 65025, UKRAINE
6003	LYSENKO, Grygorii (b) (4)	Kyiv Regional Clinical Hospital 1 Boggovutovska str Kyiv, 04107, UKRAINE
6004	PEREPELYTSYA. Mykhaylo (b) (4)	Lviv Regional State Clinical Treatment-and-Diagnostic Cardiology Center 35 Kulparkivska str Lviv, 79015, UKRAINE
6005	RUDYCK, Yuriy (b) (4)	Institute of Therapy of AMS of Ukraine, 2a Postysheva avenue Kharkiv, 61039, UKRAINE
6006	TRYSHCHUK, Nadiya (b) (4)	Clinical Hospital n.a. Meschaninova 3 Balakireva square Kharkiv, 61018, UKRAINE
6007	TSELUYKO. Vera (b) (4)	Kharkiv city Clinical Hospital #8 266 g Saltovskoe shosse Kharkiv, 61178, UKRAINE
6008	YAGENSKY. Andriy (b) (4)	Lutsk City Hospital 13 Pr. Vidrodenia Lutsk, 43024, UKRAINE

Table 4: CL2-05985-005 Investigators (cont.)

Site #	Investigator(s)	Address
7000	FARSANG, Csaba (b) (4)	St Imre Hospital Cardiometabolic center Tetenyi ut 12-16 1115 Budapest
7001	KOVACS, Aranka (b) (4)	Dr. Buygyi Istvan hospital Szentes Sima Ferenc utca 44-58 6600 SZENTES, HUNGARY
7002	VERTES, Andras (b) (4)	Szent Istvan Hospital 1st Department of Internal Medicine Nagyvarad ter 1 1096 BUDAPEST, HUNGARY
7003	ZILAH, Zsolt	Medi-Pharma 98 Ltd Kassa utca 39 4400 NYIREGYHAZA, HUNGARY
7005	KAPOCSI, Judit (b) (4)	Szent Imre Hospital Cardiometabolic center Tetenyi ut 12-16 1083 BUDAPEST, HUNGARY
7006	PALL, Denes (b) (4)	University of Debrecen 1st Department of Internal Medicine Nagyerdei krt 98 4012 DEBRECEN, HUNGARY

Table 5: X985400 Investigators

Site #	Investigator(s)	Address
0561	BUCHANANAN, Patricia (b) (4)	Willamette Valley Clinical Studies 890 River Road Eugene, OR 97404
0564	ARMAS, Eddie (b) (4)	Well Pharma Medical Research Corp 7000 Southwest 62nd Avenue Suite 405 & 100 Miami, FL 33143

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0571	LYND, Sean (b) (4)	IVA Research 948 Old State Route 74, Suite 1 Cincinnati, OH 45245
0574	SERFER, Harry (b) (4)	S&W Clinical Research 2510 East Oakland Park Boulevard Fort Lauderdale, FL 33306
0577	PAMPE, David (b) (4)	MetaClin Research, INC. – Austin 5815 West William Cannon Drive Suite 103 Austin, TX 78749
0578	POSS, Geri (b) (4)	1148 East Commerce Street San Antonio, TX 78205
0579	AHMED, Azazuddin (b) (4)	2555 South Dr. Martin Luther King Drive 2nd Floor Chicago, IL 60616
0580	UNGER, Jeffrey (b) (4)	Catalina Research Institute, LLC 14726 Ramona Avenue, Suite 100 Chino, CA 91710

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0581	HILL, John  (b) (4)	Avail Clinical Research, LLC 860 Peachwood Drive DeLand, FL 32720
0589	PULLMAN, John  (b) (4)	Big Sky Clinical Research 300 West Mercury Street Butte, MT 59701
0615	ISAKOV, Terence  (b) (4)	5187 Mayfield Road, Suite 103 Lyndhurst, OH 44124
0617	KESSEL, John  (b) (4)	PMG Research of Hickory, LLC 1985 Startown Road Hickory, NC 28602

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0618	WILSON, Jonathan (b) (4)	PMG Research of Winston-Salem 1901 South Hawthorne Road Suite 306 Winston-Salem, NC 27103
0631	LEWIN, Andrew (b) (4)	National Research Institute 2010 Wilshire Boulevard, Suite 302 Los Angeles, CA 90057
0633	CORDER, Clinton (b) (4)	COR Clinical Research 1211 North Shartel, Suit 802 Oklahoma City, OK 73103
0644	TOTH, Phillip (b) (4)	Midwest Institute For Clinical Research 8803 North Meridian Street Suite 200 Indianapolis, IN 46260
0647	JONES, Enrico (b) (4)	Traid Clinical Trials, LLC 515 College Road, Suite 15 Greensboro, NC 27410
0648	KERZNER, Boris (b) (4)	Health Trends Research, LLC 2700 Quarry Lake Drive, Suite 240 Baltimore, MD 21209

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0649	LACOUR, Audrey (b) (4)	Juno Research, LLC – Houston 9119 South Gessner, Suite 107 Houston, TX 77074
0650	O’BARR, Thomas (b) (4)	Sestron Clinical Research 1810 White Circle, Suite 125 Marietta, GA 30066
0651	TORO, Hugo (b) (4)	Juno Research, LLC – Katy 607 South Mason Road Katy, TX 77450
0652	HART, Terence (b) (4)	203 West Avalon Avenue, Suite 390 Muscle Shoals, AL 35662
0653	HASSMAN, David (b) (4)	Comprehensive Clinical Research 175 Cross Keys Road Centennial Center, Building 300-B Berlin, NJ 08009
0654	STROUT, Cynthia (b) (4)	Coastal Carolina Research Center 1156 Bowman Road, Suite 102 Mount Pleasant, SC 29464

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0655	BERNSTEIN, Richard (b) (4)	Marin Endocrine Care & Research Inc 900 South Eliseo Drive, Suite 201 Greenbrae, CA 94904
0656	BROKER, Robert (b) (4)	Hillcrest Clinical Research, LLC 717 Southeast Main Street, Suite B Simpsonville, SC 29681
0657	WEISS, Robert (b) (4)	Maine Research Associates 300 Main St Lewiston, ME 04240
0658	RANDALL, William (b) (4)	PriMed Clinical Research 540 Lincoln Park Boulevard Kettering, OH 45429
0659	DAWSON, Cara (b) (4)	Horizons Clinical Research Center LLC 4495 Hale Parkway, Suite 101 Denver, CO 80220
0660	COMIANOS, Marc (b) (4)	Frederick C Smith Clinic, Inc 1040 Delaware Avenue Marion, OH 43302

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0661	BAYS, Harold (b) (4)	L-MARC Research Center 3288 Illinois Avenue Louisville, KY 40213
0662	BLUMENAU, Joe (b) (4)	Research Across America 9 Medical Parkway, Suite 202 Dallas, TX 75234
0663	MORCOS, Nabil (b) (4)	Research Across America 999 North Tustin Avenue, Suite 120 Santa Ana, CA 92705
0664	SANDOVAL, Jamie (b) (4)	1301 Santa Fe Street, Suite B Corpus Christi, TX 78404
0665	WHITE, Alexander (b) (4)	5111 Ridgewood Avenue, Suite 301 Port Orange, FL 32127

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0666	LUBIN, Barry (b) (4)	Nathonal Clinical Research-Norfolk Inc 885 Kempsville Road, Suite 221 Norfolk, VA 23502
0667	SEGER, William (b) (4)	4504 Boat Club Road, Suite 400A Fort Worth, TX 76135
0668	JEANFREAU, Robert (b) (4)	3800 Houma Boulevard, Suite 345 Metairie, LA 70006

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0669	ROTH, Eli  (b) (4)	Sterling Research Group, Ltd 2230 Auburn Avenue, Level B Cincinnati, OH 45219
0670	HULING, Randall  (b) (4)	Olive Branch Family Medical Center 9075 Sandidge Center Cove Olive Branch, MS 38654
0671	KLEIN, Thomas  (b) (4)	Heartland Research Associate, LLC 1709 South Rock Road Wichita, KS 67207

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0672	MCKENNEY, James (b) (4)	National Clinical Research-Richmond Inc 2809 Emerywood Parkway Suite 140 Richmond, VA 23294
0673	RUBINO, John (b) (4)	3521 Haworth Drive, Suite 100 Raleigh, NC 27609
0673	ROMERO, Alicia (b) (4)	3521 Haworth Drive, Suite 100 Raleigh, NC 27609
0674	MARPLE, Richard (b) (4)	Castlerock Clinical Research Consultants, LLC 6804 South Canton, Suite 200 Tulsa, OK 74136
0675	POWELL, Stephanie (b) (4)	PMG Research of Bristol 1958 West State Street Bristol, TN 37620

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0677	AGAIBY, John (b) (4)	Clinical Investigation Specialists Inc – Gurnee 6121 Green Bay Road Kenosha, WI 53142
0678	GOETSCH, Allen (b) (4)	Clinical Research Associates 131 Longwood Drive Huntsville, AL 35801
0679	PLEVIN, Sanford (b) (4)	Suncoast Clinical Research, Inc Palm Harbor 3890 Tampa Road Suite 301 Palm Harbor, FL 34684
0680	GOTFRIED, Mark (b) (4)	Pulmonar Associates, PA 5750 West Thunderbird Road Building E-500 Glendale, AZ 85306
0681	LARSEN, David (b) (4)	Wasatch Clinical Research 4001 South 700 East, Suite 105 Salt Lake City, UT 84107

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0682	STEARNS, Pamela (b) (4)	South Florida Research Solutions LLC 601 Northwest 179 Avenue Suite 201 Pembroke Pines, FL 33029
0683	REYES, Hubert (b) (4)	MediSphere Medical Research Center, LLC 1401 Professional Boulevard Suite 100 Evansville, IN 47714
0684	BITTAR, Neville (b) (4)	Gemini Scientific, LLC 6417 Normandy Lane, Suite 208 Madison, WI 53719
0685	ALWINE, Lawrence (b) (4)	Brandywine Clinical Research 77 Manor Avenue, Suite 100 Downingtown, PA 19335

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0686	FRASER, Neil (b) (4)	Troy Internal Medicine, PC Research Department 4550 Investment Drive, Suite 210 Troy, MI 48098
0687	DIGREGORIO, Michael (b) (4)	1440 North Eastern Avenue Las Vegas, NV 89101
0688	MULLEN, Julia (b) (4)	Sterling Research Group, Ltd 650 Sprucewood Lane Erlanger, KY 41018

Table 5: X985400 Investigators (cont.)

Site #	Investigator(s)	Address
0689	PATEL, Suchet (b) (4)	Regional Clinical Research, Inc 415 Hooper Road Endwell, NY 13760
0690	WALLACE, Jesse (b) (4)	Four Rivers Clinical Research, Inc 225 Medical Center Drive, Suite 305 Paducah, KY 42003

Table 6: Financial Disclosure Information Not Obtained (CL2-05985-005 Investigators)

Site #	Investigator	Reason Financial Disclosure Not Obtained
0410	GUINET, Jean-Michel	Investigator refused to sign Financial Disclosure Form
0505	MEME, Bruno	Financial Disclosure Form never received from Investigator
0604	CURABA, Claudine	Investigator not located
0811	COTINAT, Jean- Paul	Investigator not located
1801	CLAROUX, Philippe	Financial Disclosure Form never received from Investigator
1817	NUYTS, Eric	Investigator refused to sign Financial Disclosure Form
3008	(b) (4)	Investigator is deceased
4002		Investigator did not have any patients in the study
5000		Sponsor unable to contact Investigator
5000		Sponsor unable to contact Investigator
5000		Sponsor unable to contact Investigator
5001		Sponsor unable to contact Investigator
5003		Sponsor unable to contact Investigator
5005		Sponsor unable to contact Investigator
5005		Sponsor unable to contact Investigator
5006		Sponsor unable to contact Investigator
5006		Sponsor unable to contact Investigator
5006		Sponsor unable to contact Investigator
5006		Sponsor unable to contact Investigator
5006		Sponsor unable to contact Investigator
5006		Sponsor unable to contact Investigator
5008		Sponsor unable to contact Investigator
5008		Sponsor unable to contact Investigator

**Table 6: Financial Disclosure Information Not Obtained (CL2-05985-005 Investigators)
(cont.)**

Site #	Investigator	Reason Financial Disclosure Not Obtained
5009	(b) (4)	Sponsor unable to contact Investigator
5009	(b) (4)	Sponsor unable to contact Investigator
5011	(b) (4)	Sponsor unable to contact Investigator
5011	(b) (4)	Sponsor unable to contact Investigator
5015	(b) (4)	Sponsor unable to contact Investigator
5015	(b) (4)	Sponsor unable to contact Investigator
5017	(b) (4)	Sponsor unable to contact Investigator
6003	(b) (4)	Investigator did not take part in the study

1.3.2 FIELD COPY CERTIFICATION

A field copy will not be provided to the ORA District Office as described in 21 CFR 314.440(a)(4), but a letter will be submitted certifying that the electronic CMC section has been submitted to CDER, as directed by the Office of Regulatory Affairs Memorandum dated 24 September 2003. A copy of this letter is attached.



20 March, 2014

Food and Drug Administration
Cincinnati District Office
6751 Steger Drive
Cincinnati, OH 45237

To Whom It May Concern,

Symplmed Pharmaceuticals, LLC (Symplmed) is submitting a New Drug Application (NDA) to the Food and Drug Administration (FDA) on 21 March, 2014. The NDA number is 205003 and will be submitted in electronic Common Technical Document format over the FDA's Electronic Submissions Gateway. The submission is roughly 4 GB in size.

This letter is to notify The FDA's District Office of this electronic submission as directed by the Office of Regulatory Affairs Memorandum dated 24 September 2003.

A paper copy of the Chemistry, Manufacturing, and Controls (CMC) Modules will not be provided as described in 21 CFR 314.440(a)(4). Instead, this letter is sent to certify that the electronic CMC section has been submitted to the Center for Drug Evaluation and Research.

Should you have any questions regarding this submission, please contact me at phone number or by email at emerson@symplmed.com.

Sincerely,

Erik Emerson
President and Chief Executive Officer
Symplmed Pharmaceuticals, LLC
5375 Medpace Way
Cincinnati, OH 45227

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

/s/

MARY GRACE LUBAO
01/30/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205003 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Prestalia Established/Proper Name: Perindopril arginine and Amlodipine besylate Dosage Form: Tablets		Applicant: Symplmed Pharmaceuticals, LLC Agent for Applicant (if applicable): Medpace
RPM: Wayne Amchin		Division: DCRP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p>X No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: January 14, 2015</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>January 21, 2015</u> 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 4
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	X None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	X No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	X Included
Documentation of consent/non-consent by officers/employees	X Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s)
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	X Included in Approval Letter
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	X Included in Approval Letter
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	X Included in Action Letter
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	4-22-14 4-15-14
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 1-21-15 DMEPA: <input type="checkbox"/> None 12-23-14 and 7-16-14 DMPP/PLT (DRISK): <input type="checkbox"/> None 12-12-14 OPDP: <input type="checkbox"/> None 12-12-14 SEALD: X None CSS: X None Other: X None
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	4-23; 4-27; 5-6; 5-8; 5-16; 5-20-14; 12-3-14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 12-19-14
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes X No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>12-3-14</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	3-31; 4-3; 4-17 (2); 4-30; 5-2; 6-3; 9-17; 10-22-14
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 11-4-13 <input type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A 11-15-12 (IND); 10-20-10 (IND)
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-12-15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-8-15
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 2858-1
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review see CDTL review 11-26-14 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	11-26-14 (Clinical review pp.21-3)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	X None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 9-22-14
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	X None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-8-15 and 11-6-14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 12-8-14
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12-8-14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	X No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8-4-2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	X None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	X No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	X No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11-14; 11-20; 12-23-14
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 5-16-14
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
X Review & Environmental Impact Statement <i>(indicate date of each review)</i>	9-30-14
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 12-23-14 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	X Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	X Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	X Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	X Done
❖ Ensure Pediatric Record is accurate	X Done
❖ Send approval email within one business day to CDER-APPROVALS	X Done

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/s/

WAYNE S AMCHIN
01/21/2015

**PeRC PREA Subcommittee Meeting Minutes
December 3, 2014**

PeRC Members Attending:

Wiley Chambers

George Greeley

Kevin Krudys

Dionna Green

Dianne Murphy

Kristiana Brugger

Colleen LoCicero

Julia Pinto

Greg Reaman ((b) (4))

Hari Cheryl Sachs

Michelle Roth-Cline

Karen Davis-Bruno

Peter Starke

Olivia Ziolkowski

Rosemary Addy

Barbara Buch

Nisha Jain ((b) (4))

Adrienne Hornatko-Munoz ((b) (4))

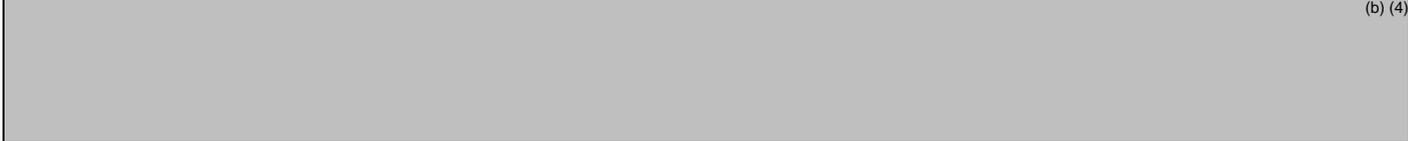
PREA



(b) (4)

	<i>NDA</i>	<i>205003</i>	<i>Prestalia (perindopril arginine/amlodipine besylate) Full Waiver</i>	<i>Treatment of hypertension</i>
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(b) (4)



(b) (4)

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Prestalia (perindopril arginine/amlodipine besilate) Full Waiver

- Proposed Indication: Treatment of hypertension
- This application triggered PREA as a new active ingredient.
- The PDUFA goal date is January 21, 2015
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a full waiver because product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients.

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/s/

GEORGE E GREELEY
12/22/2014



NDA 205003

INFORMATION REQUEST

Symplmed Pharmaceuticals, LLC
Attention: Erik Emerson
President and Chief Executive Officer
c/o Medpace Inc.
5375 Medpace Way
Cincinnati, OH 45227

Dear Mr. Emerson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prestalia (Perindopril arginine/Amlodipine besylate) tablets in doses of 3.5/2.5 mg, 7/5 mg, and 14/10 mg for the treatment of hypertension.

We are reviewing the Clinical Pharmacology section of your application and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Based on your responses to our information requests submitted on June 27, September 12 and September 23, 2014, we are unable to establish an unequivocal PK bridge between the exposure to perindopril in your proposed fixed-dose combination product and ACEON[®]. At worst, exposures to perindopril could be about twice as high with the fixed combination than with ACEON[®]. From a labeling perspective, a clear understanding of the relative bioavailability of your product is essential to rely upon certain sections of the ACEON[®] product insert, and specifically to rely upon information related to use in elderly patients and patients with renal impairment, who require dose adjustment because of increased exposure.

To address this issue, we believe you need to conduct a bioequivalence study between your proposed fixed-dose combination product (perindopril arginine/amlodipine) and ACEON[®] (perindopril erbumine). The analytes that should be quantified in this study are perindopril and perindoprilat. The primary analysis should be the comparative bioavailability in the exposure to perindopril with the comparison of perindoprilat serving as supportive evidence. As a best practice and for completeness of information from this study, we suggest including NORVASC[®] in this study and establishing a PK bridge for amlodipine.

If you have any questions, please contact me at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Wayne Amchin
Senior Consumer Safety Officer
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WAYNE S AMCHIN
10/22/2014

From: [Weisshaar, Pamela](#)
To: [Knight, Yvonne](#); [Amchin, Wayne](#)
Cc: [Breen, Dennis L.](#); [Erik Emerson \(emerson@symplmed.com\)](mailto:emerson@symplmed.com); [Dale, Kelli](#); [Bouie, Teshara](#)
Subject: RE: Information Request for NDA 205003 (Prompt Response)
Date: Wednesday, September 17, 2014 4:19:27 PM

Thank you, Yvonne. I have received your request.

Pam

Pamela S. Weisshaar

Manager, Regulatory Affairs

Medpace

5375 Medpace Way

Cincinnati OH, 45227

Tel: +1.513.579.9911, ext. 2505

Mobile: (b) (4)

Fax: +1.513.579.0444

E-mail: p.weisshaar@medpace.com

www.medpace.com

From: Knight, Yvonne [mailto:Yvonne.Knight@fda.hhs.gov]

Sent: Wednesday, September 17, 2014 4:18 PM

To: Weisshaar, Pamela; Amchin, Wayne

Cc: Breen, Dennis L.; Erik Emerson (emerson@symplmed.com); Dale, Kelli; Bouie, Teshara

Subject: RE: Information Request for NDA 205003 (Prompt Response)

Importance: High

Hi Pam,

Unfortunately the response you provided still did not include the statement we requested.

Environmental Assessment statement per 21 CFR 25.15(d) that informs the Agency that “*to your (Sponsor/Applicant’s) knowledge, no extraordinary circumstances exist.*”

Please provide the statement by **COB Thursday September 18, 2014**. Note: I will be out of the office until early next week so please cc Ms. Teshara Bouie on your correspondence as well.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight

From: Weisshaar, Pamela [mailto:P.Weisshaar@Medpace.com]

Sent: Wednesday, September 17, 2014 11:49 AM

To: Knight, Yvonne; Amchin, Wayne

Cc: Breen, Dennis L.; Erik Emerson (emerson@symplmed.com); Dale, Kelli

Subject: FW: Information Request for NDA 205003 (Prompt Response)

Importance: High

Dear Yvonne,

On behalf of Symplmed Pharmaceuticals, Medpace is providing this response to the Information request received for NDA 205003 via email on 16 September 2014.

The attached file contains the Statement of Categorical Exclusion per 21 CFR 25.31(b) for Prestalia.

This file will be submitted to the NDA over the electronic submissions gateway this afternoon.

If you have any questions regarding this submission, please contact me by email or phone.

Best Regards,
Pam

Pamela S. Weisshaar

Manager, Regulatory Affairs

Medpace

5375 Medpace Way

Cincinnati OH, 45227

Tel: +1.513.579.9911, ext. 2505

Mobile: (b) (4)

Fax: +1.513.579.0444

E-mail: p.weisshaar@medpace.com

www.medpace.com

From: Erik Emerson [<mailto:emerson@symplmed.com>]

Sent: Tuesday, September 16, 2014 1:20 PM

To: Weisshaar, Pamela

Subject: Fwd: Information Request for NDA 205003 (Prompt Response)

Importance: High

Erik Emerson
President & CEO
Symplmed Pharmaceuticals

(b) (4)

----- Original message -----

From: "Knight, Yvonne"

Date: 09/16/2014 11:13 AM (GMT-05:00)

To: emerson@symplmed.com

Subject: Information Request for NDA 205003 (Prompt Response)

Good morning Mr. Emerson,

We have an information request concerning Symplmed' s New Drug Application (NDA) for NDA 205003. We request a prompt response to this IR request no later than **Wednesday COB September 17, 2014.**

We are reviewing the categorical exclusion section of your submission but we are unable to locate the Environmental Assessment statement per 21 CFR 25.15(d) that informs the Agency that *“to the applicant's knowledge, no extraordinary circumstances exist.”*

1. Please either provide the statement or provide a response to where it can be found in the contents of your submission.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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MPUID5375

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/s/

YVONNE L KNIGHT
09/17/2014

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

/s/

SHARON K GERSHON
07/28/2014

SUSAN D THOMPSON
07/28/2014



NDA 205003

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Symplmed Pharmaceuticals, LLC
Attention: Erik Emerson
President and Chief Executive Officer
c/o Medpace Inc.
5375 Medpace Way
Cincinnati, OH 45227

Dear Mr. Emerson:

Please refer to your New Drug Application (NDA) dated March 21, 2014, received March 21, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Prestalia (Perindopril arginine/Amlodipine besylate) tablets in doses of 3.5/2.5 mg, 7/5 mg, and 14/10 mg for the treatment of hypertension.

We also refer to your amendments dated April 4, 8, 25, May 5, 6, and 15, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 21, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 19, 2014.

During our filing review of your application, we identified the following potential review issues:

REGULATORY

1. The bridge to support reliance on Aceon[®] and Norvasc[®] appears to be based, in part, on information contained in one listed drug's summary basis of approval (SBA), which is not also reflected in that drug's approved labeling. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(2) NDAs. The SBA and FDA reviewers' public summaries do not constitute full reports of investigations. See 21 C.F.R. 314.430(e)(2). Please note that a 505(b)(2) applicant that seeks to rely on the Agency's finding of safety and/or effectiveness for listed drugs may rely on FDA's finding of safety and effectiveness as reflected in the FDA approved labeling for the listed drugs, but not the SBA.

CLINICAL

2. The submission seeks approval of Prestalia[®] in three strengths: 3.5/2.5 mg, 7/5, and 14/10 mg. Prestalia (7/5 mg) was not evaluated in either study X985400 or CL2-05985-005). Hence, there are no data that directly address the effectiveness or safety of this dose as compared with the low and high dose combinations. Therefore, it is unclear how prescribing information for Prestalia[®] can provide adequate instructions for use of the 7/5-mg dose. It is insufficient to know that it must be effective, because it lies between two effective doses; it needs to have some rationale in the titration to a target blood pressure.
3. The lack of a placebo arm (or 24-hour ambulatory blood pressure data which do not appear to be susceptible to a placebo effect) in Study X985400 (PATH) does not allow us to compare the effect size of the lower dose combination (perindopril arginine/amlodipine besylate 3.5/2.5) tested in Study CL2-05985-005 with the higher dose combination (perindopril arginine/amlodipine besylate 14/10 mg) tested in Study X985400 (PATH).

CHEMISTRY, MANUFACTURING AND CONTROLS

4. Section 3.2.S. is incomplete; the current information available for both drug substances should be provided in 3.2.S.1, 3.2.S.2 and 3.2.S.3 with references to the DMFs, where appropriate for additional details. Basic aspects (e.g., physico-chemical properties, structures, etc.) should be included in the NDA, along with a relevant discussion of those attributes that are critical to the manufacture and stability of the drug product.
5. A master batch record for drug product manufacture is not provided in the application. Either submit a master batch record to the NDA or provide a statement indicating that the process described in the executed batch records will be followed for all commercial batches.
6. Your compatibility studies for the drug substances with the excipients used in the manufacture of the drug product do not detect whether any interactions occur between excipients and the (b) (4) of the drug substances.

Provide data to demonstrate that the (b) (4) components of the drug substances do not interact with the excipients of the drug product under manufacturing conditions or alternatively, provide tests in the drug product specification to quantify these two components in the finished product.

7. Provide a more detailed description of how (b) (4) is determined and controlled in the commercial drug product process.
8. Revise the container labels and package insert information to make clear that the tablet strength for amlodipine besylate corresponds to the amount of the free base and not the besylate salt. A separate equivalency statement should also be included on the container labels to indicate the amount of amlodipine besylate in the tablets.

BIOPHARMACEUTICS

9. The dissolution profile comparisons conducted to support the approval of the lower strengths failed the similarity criteria (i.e., $F2 < 50$), suggesting lack of dose proportionality. Address the clinical relevance of the lack of dose-proportionality.
10. The dissolution profile comparisons conducted to support the bridge between the clinical studies conducted by Servier outside the US and the clinical studies conducted by XOMA in the US failed the similarity criteria (i.e., $F2 < 50$) in pH 6.8 medium. Address the clinical relevance of these findings.
11. Your proposed acceptance criteria of $Q = \frac{(b)}{(4)}\%$ in 15 min for both components is not supported by the data. Pending the additional data to support the approval of the dissolution method, we recommend an acceptance criteria of $Q = \frac{(b)}{(4)}\%$ in 15 min for both components.

CLINICAL PHARMACOLOGY

12. The adequacy of the bridge between your fixed-dose combination product (perindopril arginine/amlodipine besylate) and the US approved monotherapies, and specifically, the approved monotherapy Aceon[®] (perindopril erbumine) is a review issue. Cross-study comparisons indicate that the 90% confidence intervals of the geometric mean ratios of the exposure measures for perindopril and perindoprilat between the to-be-marketed highest strength of your fixed-dose combination and Aceon[®] fall outside of usual bioequivalence limits.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

In addition, we have the following comments and requests for information:

1. If you seek an initial therapy claim, then for Studies X985400 (PATH) and CL2-05985-005, submit the following graphs by study and treatment group:
 - Probability of Achieving SBP < 140 mm Hg
 - Probability of Achieving SBP < 130 mm Hg
 - Probability of Achieving DBP < 90 mm Hg
 - Probability of Achieving DBP < 80 mm Hg
2. Submit the following information:
 - a) The solubility profile in the physiologically relevant pH for both components.
 - b) Dissolution method report justifying the selection of the proposed dissolution medium and its volume (i.e., 1000 mL) for both components of your product. For this purpose, provide dissolution profiles as a function of medium and pH for both perindopril arginine and amlodipine besylate.
 - c) List of the critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution with supporting data.
 - d) Dissolution data for both components supporting the discriminating ability of the dissolution method towards the CMAs and/or CPPs.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. The length of Highlights (HL) must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement).
2. The horizontal line bracketing each heading in HL should extend over the entire width of the column. The horizontal line for Warnings and Precautions does not extend the full width.

3. The product title in the HL section following the Highlights Limitation Statement should not be in all UPPER CASE.
4. The first sentence of your Indications and Usage statement should say Prestalia is a fixed-dose combination of perindopril, an angiotensin converting enzyme inhibitor, and amlodipine, a dihydropyridine calcium channel blocker, indicated for the treatment of hypertension.
5. In the Full Prescribing Information Table of Contents, all Section Headings should be UPPER CASE.
6. In the Full Prescribing Information Table of Contents, all subsection headings should be in Title Case. Your proposed Prescribing Information has subsection 14.1 in all UPPER CASE
7. The title of Subsection 2.2 does not match in the Table of Contents and in the Full Prescribing Information.
8. The Boxed Warning in the Full Prescribing Information does not include the section heading and it lists subsection 5.5 twice. It should say: [*see Warnings and Precautions (5.5)*].
9. Section 17 Patient Counseling Information of the Full Prescribing Information must reference any FDA-approved patient labeling. The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

In addition, you have included a subsection 17.2, FDA-Approved Medication Guide. It does not appear that you have a Medication Guide. The additional labeling document you have included is labeled as Instructions for Use. A Medication Guide, Patient Information, and Instructions for Use are different kinds of FDA-approved patient labeling. It appears that what you alternately refer to as a Medication Guide and Instructions for Use is actually Patient Information. Please clarify what kind of patient labeling you are seeking approval for and accurately reflect that in the HL and TOC, in Section 17 of the FPI, and on the patient labeling document itself.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 24, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
06/03/2014

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:

FDA/CDER/Division of Cardiovascular and Renal Products
10903 New Hampshire Avenue, Building 22, Room 4168
Silver Spring, MD 20993-0002

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Transmitted to FAX Number

Or secure email address:

D.Breen@Medpace.com

Attention:

Dennis Breen

Company Name:

Symplmed Pharmaceuticals, LLC c/o Medpace

Phone:

513-579-9911 x2727

Subject:

Information Request for NDA 205003 (Xoma 985 (perindopril arginine/Amlodipine besylate))

Date:

May 2, 2014

Pages including this sheet:

3

From:

Wayne Amchin, Regulatory Project Manager

Phone:

301-796-0421

Fax:

301-796-9841

Your New Drug Application submitted on March 21, 2014 is presently under review. The following information requests could represent filing review issues unless they are addressed immediately:

1. Submit a rationale to the NDA for assuming the applicability of foreign data in the submission to the U.S. population/practice of medicine.
2. Submit a coding dictionary used for mapping investigator verbatim terms to preferred terms in a SAS transport file. The “coding dictionary” should consist of a list of all investigator verbatim terms and the preferred terms to which they were mapped.
3. Submit a statement of Good Clinical Practice that all clinical studies were conducted under the supervision of an Investigational (Institutional) Review Board (IRB) and with adequate informed consent procedures.
4. We note that you have not submitted to this NDA narratives for deaths, adverse drop-outs, or serious adverse events. These narratives should be available upon request (within two weeks of date of the request).

You may submit the information by email to Wayne.Amchin@fda.hhs.gov, followed in close proximity by official submission to your NDA. As your NDA has not yet been filed, please note that time is of the essence so that we may complete our filing review. Our filing meeting is scheduled for May 5, 2014, and the filing date, as indicated in the NDA Acknowledgement letter to you, dated, March 31, 2014, is May 20, 2014.

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/s/

WAYNE S AMCHIN
05/02/2014

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
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D.Breen@Medpace.com

Attention:

Dennis Breen

Company Name:

Symplmed Pharmaceuticals, LLC c/o Medpace

Phone:

513-579-9911 x2727

Subject:

Information Request for NDA 205003 (Xoma 985 (perindopril arginine/Amlodipine besylate))

Date:

April 30, 2014

Pages including this sheet:

4

From:

Wayne Amchin, Regulatory Project Manager

Phone:

301-796-0421

Fax:

301-796-9841

Your New Drug Application submitted on March 21, 2014 is presently under review, and we have the following information request. Please submit the following information to your NDA:

Financial Disclosures:

1. Please indicate which investigators/subinvestigators for the conducted studies are sponsor employees (including both full-time and part-time employees). Provide a table that lists these investigators/subinvestigators, the study number, the study sites, their addresses, and whether they are full-time or part-time employees. Lastly, provide us with the total number of investigators/subinvestigators that are sponsor employees.
2. Your submission states that Study CL2-05985-005 had 339 principal investigators/subinvestigators and financial disclosures were not obtained for 30 of these individuals. However, under Section 1.3.4, Financial Certification and Disclosure, the number of individuals listed in Table 4 (CL2-05985-005 Investigators) is only 307 investigators (and 30 investigators in Table 6 (Financial Information not obtained for CL2-05985-005 Investigators)). In total, your NDA includes financial disclosures for only 337 out of the reported 339 principal investigators/subinvestigators.

Further, the investigator ID for the study patients does not seem to be included in any of the data tabulation or analysis datasets, although 188 study centers screened patients per the data tabulation demog.xpt dataset.

- Please submit the information on the two investigators not included in Section 1.3.4, Financial Certification and Disclosure.
- Please resubmit the demog dataset as follows:
 - Include a column for Investigator ID.
 - Include a column that indicates which patients were randomized and which patients were screen failures.
 - Include a column that includes treatment group.
 - Include a start date and end date for treatment.
 - Include a column that indicates whether the patient completed the trial or if the patient withdrew. If the patient withdrew, specify the reason for withdrawal (e.g., adverse event, lost to follow-up, death, other, withdrawal by subject, physician decision).
 - Include a column with the date of either study completion or withdrawal from study.
 - Include a column that indicates the last contact date for the particular patient and how the contact was made (e.g., clinic, telephone etc.).
- 3. For Study X985400 (PATH), your NDA lists a total of 431 investigators and subinvestigators (including 60 investigators) in Table 5 under Section 1.3.4, Financial Certification and Disclosure. However, in the data tabulation dataset dm.xpt, only 59 investigator IDs are provided. Please clarify the discrepancy and provide the investigator ID for each investigator.

NDA 205003 Xoma 985 (Perindopril arginine/Amlodipine besylate fixed dose combination)

You may submit the information by email to Wayne.Amchin@fda.hhs.gov, followed in close proximity by official submission to your NDA. As your NDA has not yet been filed, please note that time is of the essence so that we may complete our filing review. Our filing meeting is scheduled for May 5, 2014, and the filing date, as indicated in the NDA Acknowledgement letter to you, dated, March 31, 2014, is May 20, 2014.

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/s/

WAYNE S AMCHIN
04/30/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 108233
NDA 205003

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Symplmed Pharmaceuticals, LLC
5375 Medpace Way
Cincinnati, OH 45227

ATTENTION: Erik Emerson
President and Chief Executive Officer

Dear Mr. Emerson:

Please refer to:

- Your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Perindopril Arginine and Amlodipine Besylate Tablets, 3.5 mg/2.5 mg, 7 mg/5mg, 14 mg/10 mg
- Your New Drug Application (NDA) dated and received March 21, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Perindopril Arginine and Amlodipine Besylate Tablets, 3.5 mg/2.5 mg, 7 mg/5mg, 14 mg/10 mg

We also refer to:

- Your correspondence to your IND, dated and received December 9, 2013, requesting review of your proposed proprietary name, Prestalia
- Your amendment to your December 9, 2013, correspondence, dated and received December 23, 2013
- Your correspondence, included in your March 21, 2014, NDA submission, requesting review of your proposed proprietary name, Prestalia

We have completed our review of the proposed proprietary name, Prestalia, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 9, 2013, and March 21, 2014, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Bengtson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3338. For any other information regarding this application, contact Wayne Amchin, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
04/22/2014

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
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US Mail address:

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Transmitted to FAX Number

Or secure email address:

D.Breen@Medpace.com

Attention:

Dennis Breen

Company Name:

Symplmed Pharmaceuticals, LLC c/o Medpace

Phone:

513-579-9911 x2727

Subject:

Information Request for NDA 205003 (Xoma 985 (perindopril arginine/Amlodipine besylate))

Date:

April 17, 2014

Pages including this sheet:

4

From:

Wayne Amchin, Regulatory Project Manager

Phone:

301-796-0421

Fax:

301-796-9841

Your New Drug Application submitted on March 21, 2014 is presently under review, and we have the following information request. Please submit the following information:

1. Study X985400 Requests

- Please provide the define file for the data tabulation datasets for Study X985400 in pdf format (it is currently in xml format only). There should be a summary page that includes the names of all the data tabulation datasets submitted with appropriate links, as done for the analysis datasets in the 4 April 2014 submission. At the top of each page, the name of the particular dataset should be listed, and at the bottom of each page, the page number should be included.
- Please provide the raw data before it was converted to SDTM and the define.pdf file for the raw data.

2. Study CL2-05985-005 Requests

- Please provide the define file for the data tabulation datasets in pdf format as specified above under #1, bullet 1.
- Please submit the original protocol and all amendments. In the original NDA submission, it appears you submitted only the final version of the protocol dated 11 December 2006.
- Please submit the original statistical analysis plan and all amendments
- Please provide the following information:
 - Date first and last patient were randomized
 - End date of trial
 - Date of final patient contact
 - Date of database lock
- For Study CL2-05985-005, we note that there is a substantial amount of financial disclosure information that was not obtained from the investigators. Please make every effort to address these deficits and forward us this updated information as soon as possible.

3. SAS codes

In response to our previous information request, we note that you provided the SAS code for generating the primary and secondary results in the clinical study report. Please submit the SAS code used for generating your derived datasets for Studies X985400 and CL2-05985-005.

You may submit the information by email to Wayne.Amchin@fda.hhs.gov, followed in close proximity by official submission to your NDA. As your NDA has not yet been filed, please note that time is of the essence so that we may complete our filing review. Our filing meeting is scheduled for May 5, 2014,

NDA 205003 Xoma 985 (Perindopril arginine/Amlodipine besylate fixed dose combination)

and the filing date, as indicated in the NDA Acknowledgement letter to you, dated, March 31, 2014, is May 20, 2014.

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/s/

NORMAN L STOCKBRIDGE
04/17/2014

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
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Or secure email address:

D.Breen@Medpace.com

Attention:

Dennis Breen

Company Name:

Symplmed Pharmaceuticals, LLC c/o Medpace

Phone:

513-579-9911 x2727

Subject:

Information Request for NDA 205003 (Xoma 985 (perindopril arginine/Amlodipine besylate))

Date:

April 17, 2014

Pages including this sheet:

4

From:

Wayne Amchin, Regulatory Project Manager

Phone:

301-796-0421

Fax:

301-796-9841

Your New Drug Application submitted on March 21, 2014 is presently under review, and we have the following information request. Please submit the following information:

1. *According to the FDA Study Data Specifications <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>, “The data definition tables should be provided as a single PDF file named define.pdf and placed in the appropriate study, specific analysis type or integrated summary folder in the datasets folder. ” You submitted the data definition files in excel format. Please email me a copy of the data definition tables in pdf format and amend your NDA by submitting the data definition tables in pdf format.*
2. *Please submit the SAS code and macros you used to produce primary endpoint results as well as other important secondary analysis results.*
3. *The nonclinical study numbers under the current NDA submission (as listed in Table 1 - 2.4 Nonclinical Overview) appear to be different from those submitted under IND108233. Please provide a list of corresponding study numbers between NDA 205003 and IND 108233, so that we can confirm that previous studies submitted during the IND are the same as those contained in the NDA. A table in the following format would meet the needs:*

<i>IND Study Number</i>	<i>NDA Comparable Number</i>
Study ABCIND	Study DEFNDA
Study 123IND	Study 456 NDA
Study 234IND	not submitted under NDA
Not submitted under IND	Study 345NDA

4. Please provide the raw datasets for the Phase 3 clinical Study (X985400 [PATH]) and the Phase 2 study (CL2-05985-005) with respective define files in pdf format (see bullet #2 for details).
5. Study X985400 Requests
 - a. In the original submission dated 21 March 2014, Statistical Analysis Plan Version 1.2 was provided for Study X985400. Please clarify if this is the only SAP for this study or if there were any amendments. Please submit the original SAP and all SAP amendments to the NDA.
 - b. Please provide the following information:
 - i. Date first and last patient were randomized
 - ii. End date of trial
 - iii. Date of final patient contact
 - iv. Date of database lock

NDA 205003 Xoma 985 (Perindopril arginine/Amlodipine besylate fixed dose combination)

You may submit the information by email to Wayne.Amchin@fda.hhs.gov, followed in close proximity by official submission to your NDA. As your NDA has not yet been filed, please note that time is of the essence so that we may complete our filing review. Our filing meeting is scheduled for May 5, 2014, and the filing date, as indicated in the NDA Acknowledgement letter to you, dated, March 31, 2014, is May 20, 2014.

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/s/

NORMAN L STOCKBRIDGE
04/17/2014

From: [Knight, Yvonne](#)
To: emerson@symplmed.com
Cc: [Knight, Yvonne](#)
Subject: Information Request for NDA 205003 (Prompt Response)
Date: Thursday, April 03, 2014 3:23:20 PM
Importance: High

Good Afternoon Mr. Emerson,

Per our conversation, we have an information request concerning Symplmed Pharmaceuticals' New Drug Application for (NDA) NDA 205003. We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please submit a revised 356h form that includes all *Manufacturers* for both Drug Substance and Drug Product facilities. The list should also any and all contract testing sites for both as well.
 - a. The information should include: site name, address, FEI#, contact person, contact #, contact fax, email and a list of all steps and or testing being performed.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
04/03/2014



NDA 205003

NDA ACKNOWLEDGMENT

Symplmed Pharmaceuticals, LLC
Attention: Erik Emerson
President and Chief Executive Officer
c/o Medpace Inc.
5375 Medpace Way
Cincinnati, OH 45227

Dear Mr. Emerson:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Perindopril arginine/Amlodipine besylate fixed dose combination tablets in doses of 3.5/2.5 mg, 7/5 mg, and 14/10 mg

Date of Application: March 21, 2014

Date of Receipt: March 21, 2014

Our Reference Number: NDA 205003

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 20, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

EDWARD J FROMM
03/31/2014

**Department of Health and Human Services****Public Health Service**

Food and Drug Administration
10903 New Hampshire Ave.
Building 51, Room 6257
Silver Spring, MD 20993

Erik C. Emerson
President, Founder & Chief Executive Officer
Symplmed Pharmaceuticals, LLC
5375 Medpace Way
Cincinnati, OH 45227

**RE: Symplmed Pharmaceuticals, LLC, Small Business Waiver Request # 2014.042 for
New Drug Application 205003, Amlodipine/Perindopril**

Dear Mr. Emerson:

This responds to your October 18, 2013, letter (received January 9, 2014) to Michael Jones, Food and Drug Administration (FDA), user fee staff, requesting a waiver of an application user fee under the small business waiver provision, section 736(d)(1)(D)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2014.042). You request a waiver of the fiscal year (FY) 2014² human drug application fee for a new drug application (NDA) 205003,³ amlodipine/perindopril. For the reasons described below, FDA grants the Symplmed Pharmaceuticals, LLC (Symplmed), request for a small business waiver of the application fee for NDA 205003, amlodipine/perindopril.

According to your waiver request:

- Symplmed Pharmaceuticals, LLC has fewer than 500 employees, including employees of affiliates.
- Symplmed does not have any affiliates.
- Symplmed is submitting its first human drug application.
- Symplmed does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce.
- Symplmed expects to submit NDA 205003 no later than the end of March 2014.

Under section 736(d)(1)(D) of the Act, a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate⁴ submits to FDA for review. As outlined in section 736(d)(4) of the Act,⁵ a small business is entitled to a waiver when the business meets the following criteria:

¹ 21 U.S.C. 379h(d)(1)(D).

² FY 2014 = October 1, 2013, through September 30, 2014.

³ Heather Banuelos, Hunton & Williams LLP, on behalf of Symplmed confirmed by email to Beverly Friedman, FDA user fee staff, on March 11, 2014, that the assigned NDA number for the amlodipine/perindopril product that is the subject of this waiver is NDA 205003.

⁴ "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(11)).

⁵ 21 U.S.C. 379h(d)(4).

Symplmed Pharmaceuticals, LLC

Waiver Request 2014.042

Page 2

1. The business must employ fewer than 500 persons, including employees of its affiliates.
2. The business does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce.
3. The marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA has reviewed its records, the Small Business Administration (SBA) size determination dated February 11, 2014,⁶ and the information you submitted. Considering all the relevant factors, FDA concludes that Symplmed meets the statutory requirements of the Act. Consequently, your request for a small business waiver of the application fee for NDA 205003 is granted, provided the marketing application is received by FDA before January 10, 2015, 1 year after the base date for the size determination. We have notified FDA's Office of Financial Management of this waiver decision.

FDA records show that Symplmed has not yet submitted the full NDA 205003. **Please include a copy of this letter granting your waiver with your submission of NDA 205003.** Once submitted, if FDA refuses to file the application or if Symplmed withdraws the application before it is filed by FDA, a reevaluation of the waiver will be required should the company resubmit its marketing application. If this situation occurs, Symplmed should contact this office at least 90 days before it expects to resubmit its marketing application to determine whether Symplmed continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Ashley Jones at 301-796-7900.

Sincerely,



Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

⁶ The SBA confirmed on February 11, 2014, that Symplmed is a small business with the following affiliate: Symplmed Consulting, Inc.

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2015. See instructions for OMB Statement, below.

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

**PRESCRIPTION DRUG USER FEE
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm>

1. APPLICANT'S NAME AND ADDRESS

SYMPLMED PHARMACEUTICALS LLC
Erik Emerson
5375 Medpace Way
Cincinnati
Hamilton
Oh 45227
US

**4. BLA SUBMISSION TRACKING NUMBER
(STN) / NDA NUMBER**

205-003

**2. NAME AND TELEPHONE NUMBER OF
REPRESENTATIVE**

88-5529769 101

**5. DOES THIS APPLICATION REQUIRE
CLINICAL DATA FOR APPROVAL?**

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

Prestalia (perindopril arginine/amlodipine besylate)

6. USER FEE I.D. NUMBER

PD3014108

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? YES NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
 THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

Privacy Act Notice:

This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online: <http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm>.

OMB Statement:

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
Erik Emerson 	President + CEO	3/21/2014

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
 \$0.00

Form FDA 3397 (03/12)

INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency, unless specifically exempted below. Form FDA 3397 should be placed in the first volume of the application with the application (FORM FDA 356(h)) form. Form FDA 3397 is to be completed on-line at https://userfees.fda.gov/OA_HTML/pdufaCAcdLogin.jsp. If you need assistance in completing the form call 301-796-7200 or email: userfees@fda.gov.

NOTE: Form FDA 3397 need not be submitted for:

CDER

- 505(j) applications
- Supplements to 505(j) applications
- 351(k) applications

CDER

Any supplement that does not require clinical data for approval.
Applications and supplements for:

- * Products for further manufacturing use only
- * Whole blood or blood components for transfusion
- * Bovine blood product for topical application licensed before September 1, 1992
- * A crude allergenic extract product
- * An in vitro diagnostic biological product licensed under Section 351 of the PHS Act
- * 351(k) applications

ITEM NO.	INSTRUCTIONS
1-2.	Self-explanatory
3.	PRODUCT NAME: Include generic or proper name and trade name, as applicable.
4.	BLA STN / NDA NUMBER - FOR AN ORIGINAL BIOLOGIC LICENSE APPLICATION (BLA) - Indicate the 6-digit BLA number (Submission Tracking Number (STN)) if pre-assigned, otherwise leave blank. For A SUPPLEMENT enter the BLA STN. FOR DRUG PRODUCTS: Indicate the new drug application (NDA) number. NDA numbers can be obtained by completing the information at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm .
5.	CLINICAL DATA: The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf .
6.	USER FEE I.D. NUMBER: Please include the ID number (generated when completing Form FDA 3397) on the application payment check.
7.	PRIORITY REVIEW VOUCHER: If you are redeeming a priority review voucher awarded to a sponsor of a tropical disease product application (see section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), please include the priority review voucher number assigned when the voucher was initially granted. See FDA's Guidance for Industry: Tropical Disease Priority Review Vouchers for further information. FDA's guidance can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf .
8.	EXCLUSIONS: The application is for an orphan drug product. Under section 736(a) (1) (F) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	WAIVER: Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.

[Close](#) [Print Cover sheet](#)

APPEARS THIS WAY ON ORIGINAL

**Department of Health and Human Services****Public Health Service**

Food and Drug Administration
10903 New Hampshire Ave.
Building 51, Room 6257
Silver Spring, MD 20993

Erik C. Emerson
President, Founder & Chief Executive Officer
Symplmed Pharmaceuticals, LLC
5375 Medpace Way
Cincinnati, OH 45227

**RE: Symplmed Pharmaceuticals, LLC, Small Business Waiver Request # 2014.042 for
New Drug Application 205003, Amlodipine/Perindopril**

Dear Mr. Emerson:

This responds to your October 18, 2013, letter (received January 9, 2014) to Michael Jones, Food and Drug Administration (FDA), user fee staff, requesting a waiver of an application user fee under the small business waiver provision, section 736(d)(1)(D)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2014.042). You request a waiver of the fiscal year (FY) 2014² human drug application fee for a new drug application (NDA) 205003,³ amlodipine/perindopril. For the reasons described below, FDA grants the Symplmed Pharmaceuticals, LLC (Symplmed), request for a small business waiver of the application fee for NDA 205003, amlodipine/perindopril.

According to your waiver request:

- Symplmed Pharmaceuticals, LLC has fewer than 500 employees, including employees of affiliates.
- Symplmed does not have any affiliates.
- Symplmed is submitting its first human drug application.
- Symplmed does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce.
- Symplmed expects to submit NDA 205003 no later than the end of March 2014.

Under section 736(d)(1)(D) of the Act, a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate⁴ submits to FDA for review. As outlined in section 736(d)(4) of the Act,⁵ a small business is entitled to a waiver when the business meets the following criteria:

¹ 21 U.S.C. 379h(d)(1)(D).

² FY 2014 = October 1, 2013, through September 30, 2014.

³ Heather Banuelos, Hunton & Williams LLP, on behalf of Symplmed confirmed by email to Beverly Friedman, FDA user fee staff, on March 11, 2014, that the assigned NDA number for the amlodipine/perindopril product that is the subject of this waiver is NDA 205003.

⁴ "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(11)).

⁵ 21 U.S.C. 379h(d)(4).

Symplmed Pharmaceuticals, LLC

Waiver Request 2014.042

Page 2

1. The business must employ fewer than 500 persons, including employees of its affiliates.
2. The business does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce.
3. The marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA has reviewed its records, the Small Business Administration (SBA) size determination dated February 11, 2014,⁶ and the information you submitted. Considering all the relevant factors, FDA concludes that Symplmed meets the statutory requirements of the Act. Consequently, your request for a small business waiver of the application fee for NDA 205003 is granted, provided the marketing application is received by FDA before January 10, 2015, 1 year after the base date for the size determination. We have notified FDA's Office of Financial Management of this waiver decision.

FDA records show that Symplmed has not yet submitted the full NDA 205003. **Please include a copy of this letter granting your waiver with your submission of NDA 205003.** Once submitted, if FDA refuses to file the application or if Symplmed withdraws the application before it is filed by FDA, a reevaluation of the waiver will be required should the company resubmit its marketing application. If this situation occurs, Symplmed should contact this office at least 90 days before it expects to resubmit its marketing application to determine whether Symplmed continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Ashley Jones at 301-796-7900.

Sincerely,



 Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

⁶ The SBA confirmed on February 11, 2014, that Symplmed is a small business with the following affiliate: Symplmed Consulting, Inc.



IND 108233

INITIAL PEDIATRIC STUDY PLAN ADVICE

Symplmed Pharmaceuticals LLC
c/o Medpace, Inc.
Attention: Ms. Pamela S. Weisshaar
Manager, Regulatory Affairs
5375 Medpace Way
Cincinnati, OH 45227

Dear Ms. Weisshaar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for XOMA 985: (Perindopril arginine/amlodipine besylate fixed-dose combination) for the treatment of hypertension.

We also refer to your submission dated 6, 2014, containing your request for waiver of the PREA requirements and to your amendment of your waiver request, dated January 27, 2014 to provide your waiver request in the Initial Pediatric Study Plan (iPSP) format.

We acknowledge your plan to request that FDA waive the requirement for pediatric assessments for XOMA 985: (Perindopril arginine/amlodipine besylate fixed-dose combination) for the treatment of hypertension for all pediatric age groups because it 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.

We have completed our initial review of your submission and have no comments at this time. Therefore, submit an Agreed iPSP no later than 90 calendar days from the date of this letter. Submit your Agreed iPSP in WORD and PDF formats. You will also need to submit your Agreed iPSP with your NDA.

As sponsor of this IND, you are responsible for compliance with the Act (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. If your IND is in eCTD format, submit 7-day reports electronically in eCTD format. If your IND is not in eCTD format, you may submit 7-day reports by telephone or fax;

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, contact Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

NORMAN L STOCKBRIDGE
02/03/2014



IND 108233

ADVICE/INFORMATION REQUEST

Symplmed Pharmaceuticals LLC.
c/o Medpace Inc.
Attention: Timothy P. O'Neill, PhD
Manager, Regulatory Affairs
5375 Medpace Way
Cincinnati, OH 45227

Dear Dr. O'Neill:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Xoma 985 (perindopril arginine/amlodipine besylate).

We also refer to your September 6, 2013, correspondence requesting a pre-NDA meeting to discuss the proposed content and structure of your NDA submission under the 505(b)(2) pathway for the indication of treatment of hypertension, alone or with other antihypertensive agents.

We also refer to our October 28, 2013, correspondence providing our meeting preliminary comments for our face-to-face meeting scheduled for November 4, 2013. We also refer to your November 1, 2013, submission, provided in advance by email on October 31, 2013, of clarification questions to our meeting preliminary comments.

We have the following comments, as provided to you in email on November 1 and 4, in response to your clarification questions:

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 2:

We seek clarification of the intent of the last sentence in the FDA's response ("Module 2 should include an Integrated Summary of Safety (ISS) and an Integrated Summary of Efficacy (ISE) from your two studies, Study X095400 (PATH) and Study CL2-05985-005").

As described in the pre-NDA briefing package, Symplmed intends to use Modules 2.7.3 and 2.7.4 to present the comprehensive analysis of efficacy and safety of Perindopril/Amlodipine fixed-dose combination, with a primary focus on the results from study X095400 (PATH) and study CL2-05985-005. Symplmed will provide the comprehensive analysis of efficacy and safety within these two Module 2 documents without exceeding the 400 page limit. Symplmed does not intend to conduct a formal pooling of efficacy or safety data from these two studies.

Additionally, Symplmed does not intend to provide separate Module 5 ISS and ISE reports since the efficacy and safety analyses will be presented comprehensively in Modules 2.7.3 and 2.7.4.

Does the Agency agree?

FDA Response to Clarification Question on FDA Response to Question 2: *Yes, FDA agrees with your proposal in this clarification question.*

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 5

(part 1): In the Other Important Information section (Section 3) of the Preliminary Response Letter there are pages of instructions for how to submit items requested by the Office of Scientific Investigations (OSI). Because there are no specific CFR citations, we are unclear as to whether any or all of Items I (General Study and Investigator Information), II (Subject Level Data Listings by Site), and III (Site Level Dataset) are required for NDA submission or are being requested as part of the OSI Pilot Program (Summary Level Clinical Site Data for CDER's Inspection Planning). Based on information from various sources in the public domain it appears that submission of Items I and II may be required, while those in Item III are voluntary at this time. **Is this correct?**

FDA Response to Clarification Question on FDA Response to Question 5 (part 1): *Part I and Part II of the OSI pre-NDA information request are required. Submission of Part III data is voluntary, and is being used to help pilot our Risk Based Site Selection Tool.*

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 5

(part 2): Based on information in the public domain we believe that Item I and Item II information should be located in the folder of the study from which the summary data was extracted. **Is this correct?**

FDA Response to Clarification Question on FDA Response to Question 5 (part 2): *Yes, that is correct. Item I and Item II information belong in Module 5 of the eCTD, and the files should be linked into the Study Tagging File (STF) for each study.*

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 5

(part 3): Based on information in the public domain, we believe that at this time failure to submit Item I and Item II information will not result in a 'refuse to file' but may result in additional information requests during the review cycle and/or delays in scheduling inspections. **Is this correct?**

FDA Response to Clarification Question on FDA Response to Question 5 (part 3): *Although failure to submit Item I and Item II will not result in a 'refuse to file', results from these inspections are used during review of the application. Any delay in providing access to this information might make it difficult to generate background packages needed to conduct inspections, which could delay meeting PDUFA goals and timelines for the NDA submission.*

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 5

(part 4): If our current understanding as summarized above is correct, failure to submit information Items I and II and the voluntary Item III would not constitute a 'refuse to file' issue. Symplmed therefore does not plan to submit these items at the time of NDA filing. **Does the Agency agree that this will not result in a 'refuse to file'?**

FDA Response to Clarification Question on FDA Response to Question 5 (part 4): See response above.

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 9:

We acknowledge the comments on the perindopril arginine test attributes. We wish to discuss the Agency's request to add a test attribute to verify the presence of arginine and appropriate levels to the specification for perindopril arginine (also referred to as (b) (4), the drug substance manufacturer).

There are currently three procedures in the drug substance specification that identify unequivocally perindopril arginine drug substance: specific optical rotation, infrared absorption spectrophotometry and thin-layer chromatography (TLC). The three tests are performed with comparison to a drug substance reference standard. The three procedures use different principles of identification. Although the Rf obtained from the TLC system is not regarded as specific, in accordance with the ICH Q6A guideline on specifications, the combination of the three procedures is sufficient and acceptable to allow the complete identification of perindopril arginine ((b) (4)).

Moreover, as mentioned in the ICH Q6A guideline, if the drug substance is a salt, identification of the individual ions should be tested and an identification test that is specific for the salt itself should suffice.

Regarding the presence of arginine in the drug substance, arginine is identified using the following methods:

- **Infrared absorption spectroscopy (IR):** this test is specific to the chemical structure of perindopril arginine and its physical state (polymorphism).
- **Thin Layer Chromatography:** this test allows for identification of both parts of the drug substance (perindopril and arginine).

In addition, the drug substance assay is carried out by potentiometry which is performed by volumetric titration of the primary and secondary amine groups using perchloric acid in anhydrous acetic acid. One mole of perindopril arginine contains one mole of perindopril and one mole of arginine. Therefore, perindopril arginine titration with perchloric acid titrates the three ionizing functional groups: two due to perindopril and one due to arginine.

Even though the assay by titration is not specific to the drug substance, it is justified for routine control according to the ICH Q6A guideline because assay by titration is combined with a specific assay of the related substances. Moreover, a tightened acceptance criterion has been established for titration (i.e., 98.5-101.5% of the theoretical drug substance content calculated in terms of the anhydrous and solvent-free substance). The assay limits provide an evaluation of the stoichiometry of the drug substance as part of the assay for perindopril arginine.

Taking into account the current identification tests for the drug substance and the compliance with ICH Q6A, Symplmed believes that these proposed tests are suitable to control perindopril arginine and there is no need to add an additional test method or acceptance criteria for the amount of arginine in perindopril arginine. **Does the Agency agree?**

FDA Response to Clarification Question on FDA Response to Question 9: *Yes, we agree with the justification for proposed arginine identity and quantification coverage in the drug substance specification.*

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 10:

We acknowledge the comments on the amlodipine besylate test attributes. We wish to discuss the Agency's request to add a test attribute to verify the presence of (b) (4) and appropriate levels to the specification for (b) (4).

There are currently two procedures in the drug substance specification that identify unequivocally amlodipine besylate drug substance: IR spectroscopy and liquid chromatography. Both tests are performed with comparison to a drug substance reference standard. The two procedures use different principles of identification. According to the ICH Q6A guideline on specifications, the combination of the two procedures is sufficient and acceptable to allow the complete identification of amlodipine besylate.

Moreover, as mentioned in the ICH Q6A guideline, if the drug substance is a salt, identification of the individual ions should be tested and an identification test that is specific for the salt itself should suffice.

Regarding the presence of besylate (b) (4) in the drug substance, (b) (4) is identified using the following methods:

- Infrared spectroscopy: this test is specific to the chemical structure of amlodipine besylate and of its physical state.
- High-performance Liquid chromatography (HPLC): HPLC method H4623-002 used by (b) (4) allows for identification of both parts of the drug substance (b) (4).

In addition, the drug substance assay is carried out by a specific liquid chromatography test using the area obtained from the peak due to amlodipine and expressing the content as amlodipine besylate.

Finally, it should be noted that in the current USP monograph for amlodipine besylate:

- Identification is performed using IR spectroscopy and liquid chromatography.
- There is no specific assay included in the USP monograph for the counter ion (benzene sulfonic acid). An identification by LC is performed using the relative retention time (RRT) for benzene sulfonate (RRT = 0.2).

Taking into account the current identification tests for the drug substance, the compliance of the proposed specification for amlodipine besylate with the ICH Q6A guideline, and the USP monograph principles for amlodipine besylate, Symplmed believes that the current test attributes are suitable to control amlodipine besylate and there is no need to add an additional test method or acceptance criteria for the amount of benzene sulfonic acid in amlodipine besylate.

Does the Agency agree?

FDA Response to Clarification Question on FDA Response to Question 10: Your proposal is acceptable pending review of the validation of the analytical methods to demonstrate that they are specific for determining the identity of the amlodipine and besylate. The methods will also need to demonstrate a 1:1 molar ratio of the two counter-ions.

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 14

(part 1): We wish to discuss the Agency’s request to add criteria to the drug product specification to identify the presence and levels of (b) (4). As indicated above in the Sponsor responses provided for Question 9 and Question 10, the current proposed tests and specifications for both drug substances comply with the ICH Q6A guideline and USP principles. Moreover, as (b) (4) are process-related test attributes, they are not degradation products in the drug product and their content are not expected to increase during drug product manufacturing or storage. Therefore, we do not agree that addition of tests for (b) (4) to the drug product specification is necessary because the analyses are performed as part of the respective drug substance specifications.

Therefore, Symplmed does not believe that adding additional test criteria to the drug product specification to identify the presence and levels of (b) (4) is APPEARS THIS determinations are part of the respective drug substance specifications. Does the Agency agree with our rationale?

FDA Response to Clarification Question on FDA Response to Question 14 (part 1):
We do not agree. Since (b) (4) are necessary parts of the drug substance, we recommend quantification of their presence in the drug product as an indication they have not degraded in the drug product manufacturing process. (E.g., have they reacted with other components of the drug product formulation, thus, decreasing the proportion of salt concentration in the drug product?) Alternatively, process development data demonstrating compatibility of all components of the drug substance with all components of the drug product manufacturing process under simulated manufacturing conditions will be acceptable in lieu of this release testing.

Symplmed Pharmaceuticals LLC clarification question on FDA Response to Question 14

(part 2): We would like to discuss further the Agency’s recommendation that we change the labeled dose strength for each drug product to reflect the level of perindopril free acid rather than the level of perindopril arginine. To facilitate this discussion, a summary of the dosage strengths of perindopril in XOMA 985 and perindopril arginine products marketed worldwide except for the US and perindopril erbumine in ACEON is shown in Table 1.

Table 1 Dosage Strength Equivalents of Perindopril Arginine and Perindopril Erbumine, Expressed as Salts and as Free Acid

Perindopril arginine Expressed as the salt	2.5 mg%	(b) (4)	5 mg%	7 mg*	(b) (4)	14 mg*	NA
Expressed as the acid	(b) (4)	(u) (4)	(b) (4)	(b) (4)	(u) (4)	(b) (4)	(b) (4)
							-

Perindopril erbumine Expressed as the salt <i>Expressed as the acid</i>	2 mg ^Δ (b) (4)	(b) (4)	4 mg ^Δ (b) (4)	(b) (4)	8 mg ^Δ (b) (4)	(b) (4)	16 mg ^{Δ†} -
*Doses of perindopril arginine, expressed as the arginine salt, are those proposed for the XOMA985 fixed-dose combination product. ^g Approved doses of perindopril arginine, expressed as the arginine salt, available worldwide except in the US. ^Δ Approved doses of perindopril erbumine, expressed as the erbumine salt, in ACEON. [†] Highest approved dose of perindopril erbumine, expressed as the erbumine salt, in ACEON. NA: Not available, i.e., dosage does not exist (theoretical equivalence)							

We recognize the current USP policy for naming salt drug substances in drug products as outlined in USP <1121> which officially went into effect in May 2013. However, the current approved perindopril-containing drug product, the Listed Drug ACEON, is labeled with the dose expressed as the salt form of the drug substance (ie, perindopril erbumine) rather than as the free acid. We therefore adopted the same approach to assigning dose to our combination product, XOMA 985 tablets for the following reasons:

- The combination has a long history of development and a similar combination product is marketed worldwide with the same approach used for labeling the dose of the combination product.
- ACEON has been marketed in the US since 30 December 1993. Currently, doses of ACEON and other drugs of this class are expressed as the amount of the salt form of the drug. Changing how the perindopril dose in XOMA 985 is expressed could create confusion on the part of physicians familiar with ACEON and create the need for physician education to familiarize them with how to apply this new method of expressing potency when transitioning patients to XOMA 985 from ACEON and other drugs of this class.
- Much of the literature and all of our source documents express the dose of perindopril in terms of the salt form.
- This issue was not raised by the Agency during our October 2010 Pre-IND meeting or during any subsequent communications from the Agency regarding the IND.

We therefore propose to continue with the current naming convention for the XOMA 985 tablets and using the current approach to expressing dose of the combination drug product for the three strengths as: 3.5/2.5 mg, 7/5 mg, and 14/10 mg (perindopril arginine/amlodipine).

Does the Agency agree?

FDA Response to Clarification Question on FDA Response to Question 14 (part 2): Yes, we agree. Using the salt name perindopril arginine is acceptable.

If you have any questions, contact Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

NORMAN L STOCKBRIDGE
11/15/2013



IND 108233

MEETING PRELIMINARY COMMENTS

Symplmed Pharmaceuticals LLC.
c/o Medpace Inc.
Attention: Timothy P. O'Neill, PhD
Manager, Regulatory Affairs
5375 Medpace Way
Cincinnati, OH 45227

Dear Dr. O'Neill:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Xoma 985 (perindopril arginine/amlodipine besylate).

We also refer to your September 6, 2013, correspondence requesting a pre-NDA meeting to discuss the proposed content and structure of your NDA submission under the 505(b)(2) pathway for the indication of treatment of hypertension, alone or with other antihypertensive agents.

Our preliminary responses to your meeting questions are enclosed.

Please send me a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting, at least one business day in advance of the meeting.

If you have any questions, call me at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Wayne Amchin
Senior Consumer Safety Officer
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 4, 2013, 3-4:30pm
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 108233
Product Name: Xoma 985 (perindopril arginine/amlodipine besylate)
Indication: treatment of hypertension
Sponsor/Applicant Name: Symplmed Pharmaceuticals LLC.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for the November 4, 2013, 3-4:30pm meeting at the FDA White Oak campus between Symplmed Pharmaceuticals LLC and the Division of Cardiovascular and Renal Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the me to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

Symplmed Pharmaceuticals LLC requested this pre-NDA meeting to discuss and seek Agency agreement on the proposed content and structure for an NDA submission using the 505(b)(2) pathway for Xoma 985, a fixed-dose combination of perindopril arginine, an ACE inhibitor, and amlodipine besylate, a calcium channel blocker, 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 tert-butylamine 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.

2. DISCUSSION

2.1. Clinical

Question 1: Does the Agency agree that the organizational structure described in the proposed Modules 2.7.3 and 2.7.4 tables of contents are acceptable?

FDA Response to Question 1: Yes.

Question 2: Does the Agency agree that the proposed efficacy and safety analyses, the presentation of efficacy and safety results, and the integration strategies within Modules 2.7.3 and 2.7.4 are acceptable?

FDA Response to Question 2: The proposed efficacy and safety analyses are acceptable; however, since you have two positive studies there is no need to include information from the literature to support efficacy and safety. Instead the information from the literature could be provided in the reference section. Module 2 should include an Integrated Summary of Safety (ISS) and an Integrated Summary of Efficacy (ISE) from your two studies, Study X0954000 (PATH) and Study CL2-05985-005.

Question 3: Symplmed intends to submit Case Report Forms (CRFs) only for patients who died, experienced an SAE, or withdrew due to an adverse event from the clinical studies submitted in support of this NDA. Does the Agency agree?

FDA Response to Question 3: Yes.

Question 4: Symplmed plans to include fully compliant Data Tabulation and Analysis datasets for the X985400 (PATH) study. Symplmed also plans to include the datasets and

annotated CRFs from study CL2-05985-005 (conducted in Europe). The Data Tabulation datasets from study CL2-05985-005 do not follow SDTM and the analysis datasets from this study do not follow ADaM. Does the Agency agree that it will be acceptable to prepare the datasets following neither SDTM nor ADaM but with appropriate define.xml files, to be submitted in support of this NDA?

FDA Response to Question 4: We prefer that you prepare the datasets following SDTM and ADaM. However, if you have finished or are close to finishing the statistical analyses, please document how the analysis datasets are derived so that we will be able to trace the derivation of the study variables in these datasets.

2.2. Biopharmaceutics and Clinical Pharmacology

Question 5: Does the Agency agree that the studies of in vitro dissolution and clinical pharmacology provide the information requested, and reflect the guidance received at the 20 October 2010 pre-IND meeting and in the 13 November 2012 written responses, and will be sufficient for this 505(b)(2) NDA submission?

FDA Response to Question 5: The 505(b)(2) approach requires bridging through PK to the reference listed drugs. A cross-study comparison of the relative bioavailability of XOMA 985 to ACEON and NORVASC is acceptable. Note that dissolution profiles comparison between Xoma 985 and the mono-products are not appropriate to support the bridging.

We remind you that the approval of the lower strengths should be supported by the following information:

- Dose-proportionality study
- Alternatively, the submission of BA/BE information for lower strengths of your proposed product may be waived if the following CFR requirements are met:
 1. Inclusion of the biowaiver request as part of the NDA submission;
 2. The lower strengths and higher strength product have the same dosage form;
 3. There is BA/BE data for the highest strength;
 4. The lower strengths product is proportionally similar in its active and inactive ingredients to the highest strength product;
 5. The lower and highest strength products have the same drug release mechanism; and
 6. Dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements.

As stated on written responses dated Nov 13, 2012, a biowaiver for a bioequivalence study to bridge the clinical studies conducted by Servier ex-US and the clinical studies conducted by XOMA in the US due to different manufacturers may be granted if the following are met:

- Inclusion of the biowaiver request as part of the NDA submission;
- The products are manufactured using the same manufacturing process and equipment;
- The test and reference products are proportionally similar in their active and inactive ingredients;

- Multi-point dissolution profile comparisons are performed using an appropriate dissolution method for all strengths manufactured at the new site. The dissolution profile of the drug product manufactured at the current and proposed sites should meet the f2 similarity test. If the dissolution method has not been approved, then dissolution profile comparisons in three different media representing the physiological pH range are recommended.

2.3. Nonclinical

Question 6: With the exception of the report for study 6678, the final nonclinical study reports identified within the table of contents of Module 2.6, in support of this NDA have been submitted to the IND. The report for study 6678 will be submitted with the NDA and all nonclinical study reports of studies in which the test material was ‘spiked’ with impurities or degradants of the drug product needed to qualify the levels of these substances in the drug product will be resubmitted with the NDA to facilitate an adequate review of the data. Does the Agency agree with the approach of providing the final nonclinical reports with the NDA?

FDA Response to Question 6: All nonclinical study reports submitted to IND108233, including the report for study 6678, should be submitted with the NDA (see 21 CFR 314.50).

Question 7: Given that no novel toxicities of the XOMA 985 were identified in the 13-week, oral, repeat-dose toxicity study (study 6678), Symplmed plans no further studies and will rely upon the Agency’s prior finding of safety for ACEON and NORVASC for this 505(b)(2) NDA submission. Does the Agency agree with this approach?

FDA Response to Question 7: Yes, we agree.

2.4. Chemistry, Manufacturing, and Control

Question 8: Letters of authorization for the applicable drug substance Type II Drug Master Files (DMFs) will be included in Module 1. Sections 2.3.S and 3.2.S will consist of the specifications for the drug substances (Sections 2.3.S.4 and 3.2.S.4.1). Is this acceptable?

FDA Response to Question 8: In addition to the specifications for the drug substance we recommend including batch analyses for all lots of drug substance used in the process development and clinical studies for the drug product. Describe your proposed acceptance criteria for drug substance to be used in all drug product production, and provide details for all analytical methods used in the determination of acceptability.

Question 9: The proposed commercial specifications for perindopril arginine are provided in Table 22. Does the Agency agree with the proposed test attributes for the commercial specification for perindopril arginine?

FDA Response to Question 9: The test attributes you have included so far are acceptable, in addition a test attribute to verify the presence of (b) (4) and appropriate levels is recommended. On review of impurity, degradation products and stability studies, it is possible that additional changes to attributes would be recommended. For analytical methods, all methods that are not USP or harmonized with USP, need detailed descriptions and validation reported in the application.

Question 10: The proposed commercial specifications for amlodipine besylate are provided in Table 24. Does the Agency agree with the proposed test attributes for the commercial specification for amlodipine besylate?

FDA Response to Question 10: The test attributes you have included so far are acceptable, in addition a test attribute to verify the presence of (b) (4) and appropriate levels is recommended. On review of impurity, degradation products and stability studies, it is possible that additional changes to attributes would be recommended. For analytical methods, all methods that are not USP or harmonized with USP, report detailed descriptions and validation in the application.

Question 11: Does the Agency have any comments on the proposed specifications for either drug substance?

FDA Response to Question 11: Since specified limits for potential genotoxic impurities depends on maximum daily exposure predicted by projected dosage, data to determine the genotoxic potential of all potential impurities (e.g., computational to determine structural alerts or in-vitro testing) should be included in the application, and batch analyses with discussions of levels of all potentially genotoxic impurities relative to the level of toxicological concern is recommended.

(b) (4)

FDA Response to Question 13: See the response to question 12.

Question 14: The proposed commercial tests and specifications for the drug product, XOMA 985 tablets, are provided in Table 26. Does the Agency agree with the proposed commercial test attributes for the drug product?

FDA Response to Question 14: The attributes included in the proposal are acceptable, but in addition, provide criteria to identify the presence and levels of arginine and benzene sulfonic acid. Upon review of data provided in the application with regard to impurities and degradation products, and stability data, it is possible additional attributes will be recommended.

We note that you intend to deboss the tablets with the corresponding strengths of the two drug substances. The current policy is to label the strength of a drug product based on the free acid or free base of the drug substance unless the counter ion is critical to the safety or efficacy of the drug product. Therefore, at this time, your planned deboss may not be representative of the labeled dose strength and may need to be changed.

Question 15: The stability studies for the drug product included bracketing of the proportionally similar dosage strengths of drug product (ie, perindopril arginine/amlodipine 3.5/2.5 mg, 7/5 mg, and 14/10 mg). An overview of the stability protocol and the primary registration stability batches of drug product evaluated to support an expiration dating period in the NDA are described in Section 18.3.8. Does the Agency agree that the stability plan is satisfactory to support NDA submission and to support an expiration dating period for the three strengths of XOMA 985 tablets?

FDA Response to Question 15: Your stability protocol is acceptable in terms of bracketing based on strength, but you are reminded the bracketing strategy should account for packaging configurations as well as strength. The size, fill level of the bottles and the ability of the bottle to protect the drug product from the environment should be adequately accounted for (e.g, headspace volume in bottles needs to be accounted for in bracketing) in addition to strength. The expiration dating period will be assigned by the Agency on review of the data in the application.

2.5. Additional comments: 505(b)(2) pathway

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge"

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and you intend to use your proposed comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s), then you should use the specified listed drug(s) (rather than a bioequivalent ANDA product or a non-U.S. approved version of the product) as the comparator

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also

include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX “TRADENAME”	Previous finding of effectiveness for indication X
3. Example: NDA YYYYYY “TRADENAME”	Previous finding of safety for Carcinogenicity, labeling section XXX
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of

the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. As noted in the draft guidance, for applications submitted on or after January 5, 2014, the sponsor should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted.

As indicated in our October 20, 2010, meeting minutes, issued on October 29, 2010, DCRP will entertain a request for a waiver of pediatric studies.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

In addition, the Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

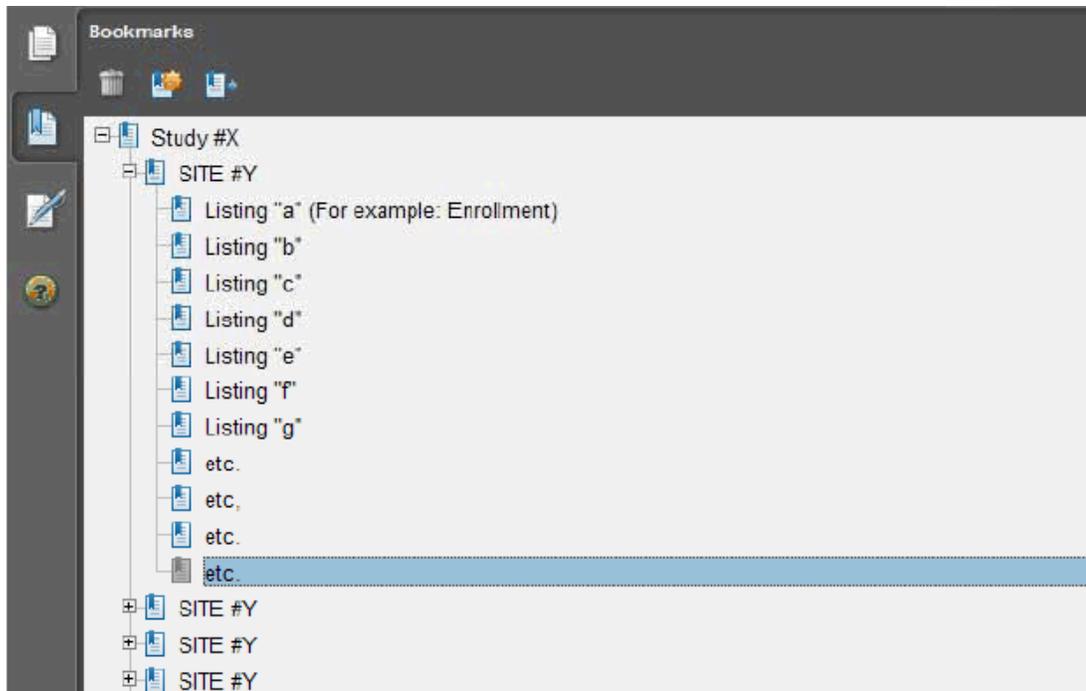
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

- d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)
 - c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 INTRODUCTION

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) – the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFSE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

INITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

WAYNE S AMCHIN
10/28/2013



IND 108233

MEETING PRELIMINARY COMMENTS

Medpace, Inc
Attn: Pamela Weisshaar
Manager, Regulatory Affairs
5375 Medpace Way
Cincinnati, OH 45227

Dear Ms. Weisshaar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for combination perindopril and amlodipine.

We also refer to your October 14, 2012, correspondence, requesting a meeting to discuss a biowaver for your product.

Our responses to your meeting questions are enclosed.

If you have any questions, please call Michael Monteleone, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc:
Xoma, LLC
2910 Seventh Street
Berkeley California, 94710

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type C
Meeting Category: Advice

Meeting Date and Time: Cancelled
Meeting Location: Cancelled

Application Number: IND 108233
Product Name: perindopril arginine/ amlodipine tablets
Indication: hypertension
Sponsor/Applicant Name: Xoma

Introduction:

This material consists of our responses to your questions and any additional comments. We believe that these responses adequately address the issues, and so we are cancelling our meeting scheduled for November 15, 2012.

1.0 BACKGROUND

In correspondence dated October 12, 2012 the sponsor requested a meeting with the Division to discuss Biowavers for their product in advance of their planned 505(b)(2) NDA submission mid-2013. Responses to the submitted questions are below.

2. DISCUSSION

Question 1: *A biowaver for comparative bioavailability study for a 505(b)(2) NDA.*

Response: Your proposal for not conducting a comparative BA study to support your proposed 505 (b) (2) submission for XOMA fixed-dose combination tablets seems reasonable. However, please note that biowaivers are not granted during IND stage. You need to submit the biowaiver request and supporting information as part of your NDA submission.

Question 2: *A biowaiver for a bioequivalence study to bridge the clinical studies conducted by Servier ex-US and the clinical studies conducted by XOMA in the US due to different manufacturers.*

Response:

The biowaiver may be granted if the following are met:

- Inclusion of the biowaiver request as part of the NDA submission;
- The products are manufactured using the same manufacturing process and equipment;
- The test and reference products are proportionally similar in their active and inactive ingredients;

- Multi-point dissolution profile comparisons are performed using an appropriate dissolution method (refer to additional Biopharmaceutics comments) for all strengths manufactured at the new site. The dissolution profile of the drug product manufactured at the current and proposed sites should meet the f2 similarity test.

If the dissolution method has not been approved, then dissolution profile comparisons in three different media representing the physiological pH range are recommended.

Question 3: *A biowaiver for a dosage form equivalence study.*

Response: The biowaiver may be granted if the following requirements are met:

- Inclusion of the biowaiver request as part of the NDA submission;
- The lower strength and higher strength product have the same dosage form;
- There are BA/BE data for the highest strength;
- The lower strength product is proportionally similar in its active and inactive ingredients to the highest strength product;
- The lower and highest strength products are manufactured at the same site and under the same process; and
- Dissolution profile comparisons between the highest and lower strengths using the QC dissolution method meet the f2 similarity requirements.

Additional Biopharmaceutics Comments

We have the following comments regarding the biopharmaceutics information that should be provided in your NDA.

- 1) **Dissolution Test:** Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
 - a. Solubility data for the drug substance covering the pH range;
 - b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;
 - c. Provide the complete dissolution profile data (individual, mean, SD, profiles) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and

- d. Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g., drug substance particle size, compression force, tablet hardness, etc.)
In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

For setting of the dissolution acceptance criterion(a) of your proposed drug product, the following points should be considered:

- a. The dissolution profile data (i.e., 15, 20, 30, 45, & 60 minutes) from the clinical pivotal batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your proposed drug product [i.e., specification-sampling time point and specification value].
- b. The in vitro dissolution profile should encompass the timeframe over which at least $\frac{(b)}{(4)}$ % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- c. The selection of the specification time point should be where $Q = \frac{(b)}{(4)}$ % dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where $Q = \frac{(b)}{(4)}$ % dissolution occurs.
- d. The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criterion for your proposed product will be made during NDA review process based on the provided data.

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

/s/

NORMAN L STOCKBRIDGE
11/13/2012

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via Email: CAFARO@xoma.com

Attention: Dan Cafaro

Company Name: XOMA (US) LLC

Phone: 510-541-5034

Subject: Meeting Minutes

Date: October 29, 2010

Pages including this sheet: 12

From: Mike Monteleone
Phone: 301.796.1952
Fax: 301.796.9841

Meeting Minutes

Application: PIND 108233
Sponsor: XOMA (US) LLC
Drug: perindopril arginine/amlodipine besylate
Type of Meeting: Pre-IND/NDA
Classification: B

Date of Meeting: October 20, 2010

List of FDA Participants:

Norman Stockbridge, MD, PhD	Director, Division of Cardio-Renal Products
Thomas Marciniak, MD	Clinical Team Leader
Preston Dunnmon, MD	Clinical Reviewer
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List of Sponsor Participants:

Jeffrey Feldstein, MD	Senior Medical Director, XOMA
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Henry Black, MD	Hypertension Consultant, Clinical Professor, NYU

Background

The Sponsor, XOMA (US) LLC is seeking the Division's advice with respect to their development plan for a fixed dose combination of perindopril arginine/amlodipine besylate for the treatment of hypertension. The sponsor has not previously submitted an IND for this drug combination, though it is currently approved and being marketed in the EU at doses of perindopril-amlodipine 5 mg-5 mg; 10 mg-5 mg; 5 mg-10 mg; 10 mg-10 mg. They would like to discuss the adequacy of available information for the submission of an NDA for the following doses of perindopril-amlodipine; 3.5 mg-

2.5 mg; 7 mg-5 mg; 14 mg-10 mg. The Division granted the sponsors meeting request on August 20, 2010 and provided preliminary comments to the sponsor's September 21, 2010 briefing package on October 19, 2010. The Division met with the sponsor on October 20, 2010, the minutes of that meeting are below.

The following questions were addressed:

Question 1:

Does the Agency agree that the proposed NDA submission should be filed using the 505(b)(2) pathway?

FDA preliminary response:

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/01p-0323-pdn0001-vol1.pdf>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug (s) or published literature that describes a specific listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Discussion during the meeting:

None.

Question 2:

It is XOMA's position that data from clinical trials CL2 05985 005, CL3 05985 006, in addition to PK, safety, and efficacy information from PKH-05985-009, CL1-06490-001, and reference to clinical trials ASCOT and STRONG, are sufficient to support the filing of an NDA for the perindopril arginine/amlodipine fixed-dose combination for the treatment of hypertension for the proposed

commercial doses of perindopril arginine/amlodipine 3.5/2.5 mg, 7/5 mg, and 14/10 mg. Does the Agency agree?

FDA preliminary response:

No, We do not agree. In order for the combination therapy to be approved, the efficacy of a combination must be demonstrated to be statistically and clinically superior to the highest approved dose levels of both mono-therapies. In other words, you must demonstrate that a combination of A+B is statistically and clinically superior to the highest doses of each monotherapy A alone and B alone. None of the referenced studies delineates the superiority of the combination product to the highest doses of each of the monotherapies.

Discussion during the meeting:

The sponsor referred to Table 1 on page 12 of their briefing package in the discussion of question 2.

Table 1 Dosage Strength Equivalents of Arginine and Erbumine Salts

Perindopril arginine (mg)	(2.5 mg)*	(b) (4)	(5 mg)*	7 mg	(b) (4)	14 mg	(b) (4)
Perindopril erbumine (mg)	2 mg ^Δ	(b) (4)	4 mg ^Δ	(b) (4)	8 mg ^Δ	(b) (4)	16 mg ^{Δ†}
<p>*Doses of perindopril arginine in parentheses () are not among those proposed for the fixed-dose combination product. ^Δ Approved doses of perindopril erbumine in ACEON. [†] Highest approved dose of perindopril erbumine in ACEON.</p>							

The sponsor discussed that a 14-mg monotherapy of perindopril arginine is not available commercially and proposed a three-arm study evaluating, 16 mg perindopril erbumine vs 10 mg amlodipine vs (14 mg perindopril arginine / 10 mg amlodipine). The sponsor stated that they would need to use two tablets for the 16-mg perindopril erbumine and would have to think about how to maintain blinding. Dr. Stockbridge agreed that the sponsor’s proposal was reasonable.

Question 3:

Trials CL2-05985-005, CL3-05985-006, PKH-05985-009, and CL1-06490-001 were conducted under Good Clinical Practices but not under US IND. What information, if any, related to the conduct of the trials is needed by the Agency in order to use these trials as the basis of the NDA?

FDA preliminary response:

We require submission of all documents and raw data related to the execution of all sponsor-executed studies, including but not limited to protocols, CRFs, statistical plans, monitoring plans, documents related to the delegation of program execution authorities to other entities, adverse event reports, and the corresponding data sets

Discussion during the meeting:

None.

Question 4:

Does the Agency have any other suggestions/requests (for analyses) of the blood pressure data from study CL3-05985-006?

FDA preliminary response:

No. Please see our response to Question 2 regarding the need to demonstrate that a combination beats both highest dosage monotherapies.

Discussion during the meeting:

None.

Question 5:

Are the numbers of patients exposed to the combination regimens at the doses studied adequate to support the NDA submission?

FDA preliminary response:

The exposures should be adequate when you complete the additional study needed.

Discussion during the meeting:

None.

Question 6:

XOMA proposes perindopril/amlodipine as initial therapy in patients with hypertension. Is this acceptable to the Agency?

FDA preliminary response:

Assessment of the benefit and risk of combination therapy as initial treatment for hypertension would necessitate a full factorial dataset throughout the entire dose range to determine the hypertension envelope where combination therapy would be justified as initial therapy. Studies 005 and 006 do not provide this information, but it could be included into the trial for assessing the higher doses of the combination as described above in our response to Question 2.

Discussion during the meeting:

Given that the sponsor proposes only a 3-arm trial testing the highest dose combination product versus the highest doses of each monotherapy (or its equivalent), Dr. Dunnmon asked the sponsor to confirm that, for the combination product, the company is no longer seeking an indication for initial therapy in patients with hypertension, and is no longer seeking an indication for patients with mild hypertension (see question 7 below). It was pointed out to the sponsor that a complete factorial study design would be needed to construct the response surface model from which the appropriateness of initial combination therapy in various patient subsets could be determined. None of the sponsor's prior non-IND studies provide this information, nor does the study design being proposed here for testing only the highest dose combination against the highest dose monotherapies. The sponsor confirmed that the company is now only seeking a second line indication for patients not responding to the monotherapies, and will not be seeking an indication for initial therapy of hypertension of (b) (4)

Question 7:

It is XOMA's position that the clinical data generated for perindopril arginine/amlodipine 3.5 mg/2.5 mg justifies its use as an optional starting dose (described in Dosage and Administration) in patients with (b) (4) based upon combination of efficacy, safety and tolerability. Does the Agency agree?

FDA preliminary response:

Please see our response to Question 6.

Discussion during the meeting:

See meeting discussion, question 6.

Question 8:

XOMA seeks regulatory guidance on the approach for inclusion of information from labels of the component drugs in the label for perindopril/amlodipine fixed-dose combination product, specifically with respect to information on clinical safety, efficacy, and drug metabolism.

FDA preliminary response:

From a 505(b)(2) regulatory perspective, you may rely on the labeling of the listed drug(s) on which your application relies on FDA's finding of safety and/or effectiveness for approval, and/or the labeling of specific listed drug(s) described in published literature on which your application relies for approval.

Discussion during the meeting:

None.

Question 9:

The labeling will indicate that the perindopril/amlodipine fixed-dose combination product has (b)
(4). XOMA plans to evaluate the US Black population after NDA approval. Is this acceptable to the Agency?

FDA preliminary response:

If approved, the absence of data in this subgroup would be reflected in the product label, within the context of potential limitations of efficacy for low renin hypertension.

Discussion during the meeting:

None.

Question 10:

Does the Agency agree that a REMS is not required and that a standard pharmacovigilance approach suffices for the perindopril/amlodipine fixed-dose product NDA?

FDA preliminary response:

It is doubtful that we would approve this product if it seems to need a REMS.

Discussion during the meeting:

None.

Question 11:

XOMA plans to request a waiver for pediatric studies with the perindopril/amlodipine fixed-dose combination product. Is this acceptable to the Agency?

FDA preliminary response:

Yes.

Discussion during the meeting:

None.

Question 12:

XOMA does not plan further clinical pharmacology/pharmacokinetic studies. Is this acceptable to the Agency?

FDA preliminary response:

No. The clinical pharmacology program is not complete. The following list of studies are required to complete the Clinical Pharmacology package (Note: Based on the Pre-NDA package, you may have some of the studies that are required) :

1. Bioequivalence study between the highest strength of perindopril erbumine proposed in the fixed-dose combination and its corresponding strength of perindopril arginine following a single oral dose in healthy volunteers. Note that in order to support NDA filing, you need to use a US marketed product of perindopril erbumine. If not, bioequivalence for perindopril erbumine has to be demonstrated with reference to the US marketed product.
2. A pharmacokinetic drug interaction study in healthy volunteers following single oral dose should be conducted at the highest dose of perindopril arginine and amlodipine. Note that in order to support NDA filing, you need to use a US marketed product of amlodipine. If not, bioequivalence has to be shown between the US marketed product of amlodipine and its equivalent comparator.
3. Bioequivalence study between highest strength of the fixed-dose combination and free combination of perindopril arginine and amlodipine has to be established following single oral dose in healthy volunteers. This study has to be prospectively powered to demonstrate bioequivalence.
4. The effect of a high fat meal on the highest strength of fixed-dose combination of perindopril arginine and amlodipine has to be submitted.

Discussion during the meeting:

The sponsor asked to clarify that in the first point in Q. 12 of Division's preliminary response, whether the perindopril salts should be reversed. The Division confirmed that they should be reversed.

In response to the Division's comment to establish bioequivalence between ACEON[®] and the European comparator, the sponsor asked if the certificate of analysis of the two products of perindopril erbumine substitute for this bioequivalence study. Dr. Srinivasachar told Dr. Madabushi that the the certificate of analysis will not provide a time-dependent release of the drug but provides a single point estimate of percentage released. Dr. Madabushi stated that *in vitro* dissolution test of the two products at extreme pH values could provide evidence of bioequivalence. The sponsor expressed concern about the amount of reserve samples they have remaining of perindopril erbumine. Dr. Stockbridge advised that it would not be necessary to use the same lots and commercially available perindopril erbumine can be used in this study. During the course of this discussion, the sponsor brought to the attention that ACEON[®] and the European comparator have the same composition of inactive excipients, but with different colorants. The sponsor commented that they would include this information in their IND.

The sponsor asked if the Division's comment number four with respect to the effect of high fat meals could be addressed in labeling by advising that the drug should be taken in the morning before breakfast, which is how they plan to conduct the trial. Dr. Stockbridge commented that

because we have reason to expect a food effect with ACEON and the relative ease with which the data can be obtained, the sponsor should study it. The sponsor asked if the food effect study could be incorporated in the high dose trial [see discussion Q2]. Dr. Stockbridge said that it could.

The sponsor summarized that they plan to begin commercial production in 2011 and plan to use commercial material in their trial. They also stated that they plan to submit their 005, 006 and 009 studies in pursuit of a second-line therapy indication.

Question 13:

XOMA does not plan further pre-clinical testing of the proposed perindopril/amlodipine fixed-dose combination product. Is this acceptable to the Agency?

FDA preliminary response:

Please remember that if you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug (s) or published literature that describes a specific listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Perindopril arginine and perindopril erbumine are different molecules. There is no toxicology information available for perindopril arginine. If perindopril arginine is dissociated from each other soon after absorbed, perindopril and arginine are unlikely to cause additional toxicity than approved perindopril erbumine. You should demonstrate and state (1) perindopril arginine is dissociated from each other soon after being absorbed, or (2) perindopril arginine and perindopril erbumine are similar in toxicology.

Impurity limits > (b) (4) % in drug substance or (b) (4) % in drug product will need to be qualified (including genotoxicity studies and general toxicity studies).

Discussion during the meeting:

The sponsor asked about the Division's last comment regarding impurities. The sponsor commented that in their calculations according to ICH Q3B, the impurity limits would be (b) (4) % for the high dose and (b) (4) % for low dose. Dr. Srinivasachar commented that if the sponsor is consistent with the ICH Q3B (R2) recommendations there should not be an issue. The sponsor also commented that they may propose higher impurity limits for the lowest strength.. Dr. Srinivasachar stated that the sponsor would have to present their case for review.

Question 14:

Are the drug substance plans for submission of data in the NDA acceptable to the Agency and does the Agency agree with the current specifications for each active ingredient?

FDA preliminary response:

ORYL Specifications for Perindopril Arginine (ORYL Type II DMF):

- The specifications for Perindopril Arginine are acceptable in general.
- However, the specification limits for impurities above (b) (4) % should be qualified according ICH Guidance Q3A.
- The limits for residual solvents acetone and toluene should be included in the drug substance specification.
- You have a separate method for Stereochemical impurities. Please clarify what impurities are referred as the stereochemical impurities.
- Provide explanation regarding the doubled chromatographic peaks for impurity (b) (4) and impurity (b) (4) are the specification limits for these impurities a total percent of doubled impurities? If not, explain what are these specification limits.
- A justification for specification limits for Particle size distribution should be provided in the NDA.

(b) (4) Type II DMF for Amlodipine besylate:



(b) (4) Specifications for Amlodipine besylate:

- The drug substance specifications should include limits for residual solvents and (b) (4)
- Additional identification test should be included according to USP monograph.
- A justification for specification limits for Particle size distribution should be provided in the NDA.

Discussion during the meeting:

None.

Question 15:

Does the Agency agree that the two proposed means of differentiating the marketed strengths of drug product (i.e., by size and debossed code) will be acceptable?

FDA preliminary response:

Differentiation of the marketed strengths of dug product by debossing code and by size is

sufficient in our opinion. However, from a medication error perspective, tablet size and strength debossing may not sufficiently differentiate a product to prevent confusion depending upon the end user. To differentiate optimally measures such as the proprietary name, strength, color, and tablet size may be used collectively to minimize confusion and medication errors.

Discussion during the meeting:

None.

Question 16:

Are the plans for the drug product stability program to be submitted to the NDA acceptable to the Agency?

FDA preliminary response:

The 6-month of long-term and accelerated site-specific stability data for three batches of each strength of the drug product manufactured at Patheon (US commercial manufacturing site) are considered as primary stability data for assignment of the expiry for drug product. It is recommended that the 12-month long-term stability data should be submitted to NDA at the time of submission. However, it may be acceptable to submit the 12-month long-term stability data not later than mid-cycle of the review time frame, i.e. 5 months before the PDUFA date. The registration stability batches should be manufactured at a scale that is at least pilot scale, and those batches should be manufactured according to the proposed commercial formulation and process; these batches should be packaged in the same container/closure as that proposed for commercial batches according to ICH Guidance Q1A(R2). The stability data from registration batches manufactured in Europe could be considered and reviewed as supportive stability data since there are number of differences between registration batches from the European site and those from US site, e.g., the packaging is different from that intended for commercial batches, and some batches of drug substance amlodipine besylate were produced by alternative synthetic route.

Discussion during the meeting:

None.

Question 17:

Are the plans for the process validation batch stability program acceptable to the Agency with the commitment that data will be provided in the annual update to the NDA?

FDA preliminary response:

The stability commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months, according to ICH Guidance Q1A (R2). The stability studies on these production batches should follow the same stability protocol as that for registration batches.

Discussion during the meeting:

None.

Signature, Meeting Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Reviewed:

MMonte Leone	21 OCT 2010 (Drafted)
LSoldatova	21 OCT 2010
KSrinivasachar	21 OCT 2010
BYang	21 OCT 2010
JKoerner	21 OCT 2010
SHariharan	22 OCT 2010
RMadabushi	26 OCT 2010
PDunmon	27 OCT 2010
TMarciniak	27 OCT 2010
EFromm	28 OCT 2010
NStockbridge	28 OCT 2010
MMonte Leone	29 OCT 2010 (Finalized)

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/s/

NORMAN L STOCKBRIDGE
10/29/2010