

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205003Orig1s000**

**CHEMISTRY REVIEW(S)**

# Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

## I. Review Cover Sheet

1. OMPQ Reviewer: Vibhakar Shah, Ph.D.
2. NDA/BLA Number: 205003  
Submission Date: 03/21/2014  
21<sup>st</sup> C. Review Goal Date: 11/21/2014  
PDUFA Goal Date: 01/21/2015

### 3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Prestalia Tablet (proposed)
Established or Non-Proprietary Name (USAN) and strength:	Perindopril arginine/Amlodipine besylate tablet
Dosage Form:	Tablet

### 4. SUBMISSION PROPERTIES:

Review Priority :	Original STANDARD (Type 4)
Applicant Name:	Symplmed Pharmaceuticals LLC
Responsible Organization (OND Division):	Division of Cardio-Renal Drug Products

## II. Application Detail

1. INDICATION: Hypertension
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 3.5/2.5 mg, 7/5 mg and 14/10 mg  
(Perindopril arginine/Amlodipine besylate)
4. Rx/OTC DISPENSED:  Rx  OTC
5. ELECTRONIC SUBMISSION (yes/no)?  Yes  No
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

### III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

<b>A. COMPLETENESS OF FACILITY INFORMATION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	X		
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	NDA 20184, Aceon Tablets, Approved on 12/10/1993

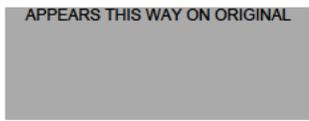
\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

<b>B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
16.	Have any Comparability Protocols been requested?		X	

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		X	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X	X	
19.	<b>From a CGMP/facilities perspective, is the application fileable?</b>  If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

APPEARS THIS WAY ON ORIGINAL



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

VIBHAKAR J SHAH  
11/26/2014

MAHESH R RAMANADHAM  
12/03/2014

**NDA 205003**

**Prestalia  
(perindopril arginine / amlodipine) tablets**

**Symplmed Pharmaceuticals, LLC**

**Charles F. Jewell Jr.  
Division of Cardiovascular and Renal Products**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary.....</b>	<b>10</b>
I. Recommendations.....	10
A. Recommendation and Conclusion on Approvability.....	10
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .....	10
II. Summary of Chemistry Assessments .....	10
A. Description of the Drug Product(s) and Drug Substance(s).....	10
B. Description of How the Drug Product is Intended to be Used .....	12
C. Basis for Approvability or Not-Approval Recommendation.....	14
III. Administrative.....	16
A. Reviewer’s Signature .....	16
B. Endorsement Block.....	16
C. CC Block .....	16
<b>Chemistry Assessment .....</b>	<b>17</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....	18
S DRUG SUBSTANCE [amlodipine besylate, (b) (4) .....	18
S DRUG SUBSTANCE [perindopril arginine, (b) (4) .....	51
P DRUG PRODUCT [XOMA 985, Tablets].....	75
A APPENDICES .....	106
R REGIONAL INFORMATION .....	106
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	107
A. Labeling & Package Insert .....	107
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	107
III. List Of Deficiencies To Be Communicated.....	107
<b>Additional Appendix.....</b>	<b>108</b>
Signatures:.....	109

# Chemistry Review Data Sheet

1. NDA 205003
2. REVIEW #: 1
3. REVIEW DATE: 14-Nov-2014
4. REVIEWER: Charles F. Jewell Jr.

## 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
SDN 1 New NDA	21-Mar-2014
Wayne Amchin – Acknowledge NDA	31-Mar-2014
Yvonne Knight – IR (Manufacturing info)	03-Apr-2014
SDN 2 Response to IR (CMC, Non-Clin)	04-Apr-2014
Wayne Amchin – Consult – Patient Labeling	04-Apr-2014
Wayne Amchin – Consult – DDMAC Labeling	04-Apr-2014
SDN 3 Response to IR (Clin)	08-Apr-2014
Janine Stewart – Proprietary Name Review	15-Apr-2014
Wayne Amchin - IR (Clinical Data Sets)	17-Apr-2014
Wayne Amchin - IR (Clinical Data Sets Further)	17-Apr-2014
Yvonne Knight - Consult - Environmental Assessment	22-Apr-2014
Karen Bengtson - Proprietary Name Granted	22-Apr-2014
Baichun Yang - Nonclinical Filing Review	23-Apr-2014
SDN 4 - Clinical-Response to IR	25-Apr-2014
Kasturi Srinivasachar - Quality Filing Review	27-Apr-2014
Wayne Amchin - IR (Financial Disclosures)	30-Apr-2014
Wayne Amchin - Consult (Clinical Inspections)	01-May-2014
Wayne Amchin - IR (Clinical)	02-May-2014
SDN 5 - Clinical - Response to IR	05-May-2014
SDN 6 - Clinical - Response to IR	06-May-2014

## Chemistry Review Data Sheet

<u>Previous Documents</u>	<u>Document Date</u>
Peter Hinderling - ClinPharm - Filing Review	06-May-2014
Jialu Zhang - BioMetrics - Filing Review	08-May-2014
SDN 7 - ClinPharm - Response to IR	15-May-2014
Bryan Riley - QualityMicro Review	16-May-2014
Karen Hicks -Clinical - Filing Review	16-May-2014
Wayne Amchin - RPM - Filing Review	20-May-2014
Wayne Amchin - COR - Filing Review Issues Identified (74-day letter)	03-Jun-2014
SDN 8 - Labeling -Package Insert Draft	18-Jun-2014
SDN 9 - Clin and ClinPharm - Response to IR	27-Jun-2014
SDN 10 - Quality and Biometrics - Response to IR	03-Jul-2014
SDN 11 - ClinPharm - Response to IR	08-Jul-2014
Janine Stewart - SURVEPI - Labeling Review	16-Jul-2014
SDN 12 ClinPharm - Response to IR	25-Jul-2014
Sharon Gershon - COR-DSICI (Clinical Inspection)	28-Jul-2014
Baichun Yang - NonClin Primary Review (approval recommendation)	04-Aug-2014
Sharon Gershon - COR-DSICI (Clinical Inspection)	04-Aug-2014
SDN 13 Quality/Stability Info	05-Aug-2014
SDN 14 Biometrics - Response to IR	06-Aug-2014
SDN 15 Clinical - Response to IR	14-Aug-2014
SDN 16 Patent & Exclusivity/Patent Cert.	18-Aug-2014
SDN 17 ClinPharm/Response to IR	25-Aug-2014
SDN 18 ClinPharm/Response to IR	03-Sep-2014
SDN 19 ClinPharm/Response to IR	12-Sep-2014
SDN 20 Quality/Response to IR	17-Sep-2014
Yvonne Knight - Environmental Assessment IR	17-Sep-2014
SDN 21 Quality/Response to IR	18-Sep-2014
Sharon Gershon - Clinical Inspection Summary	22-Sep-2014
SDN 22 ClinPharm/Response to IR	23-Sep-2014
Sharon Gershon - Clinical Inspection Summary	29-Sep-2014
James Laurenson - Environmental Assessment Review	30-Sep-2014
Sharon Gershon - Clinical Inspection Summary	30-Sep-2014
SDN 23 Quality/Response to IR	09-Oct-2014
SDN 24 General Correspondence	14-Oct-2014
SDN 25 Quality/Response to IR	16-Oct-2014
Sharon Gershon - Clinical Inspection Summary	17-Oct-2014

## 6. SUBMISSION(S) BEING REVIEWED:

## Chemistry Review Data Sheet

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SDN 1 New NDA	21-Mar-2014
SDN 2 Response to IR (CMC, Non-Clin)	04-Apr-2014
SDN 8 - Labeling -Package Insert Draft	18-Jun-2014
SDN 10 - Quality and Biometrics - Response to IR	03-Jul-2014
SDN 13 Quality/Stability Info	05-Aug-2014
SDN 20 Quality/Response to IR	17-Sep-2014
SDN 21 Quality/Response to IR	18-Sep-2014
SDN 23 Quality/Response to IR	09-Oct-2014
SDN 25 Quality/Response to IR	16-Oct-2014

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name:	Symplmed Pharmaceuticals, LLC
Address:	5375 Medpace Way Cincinnati, OH 45227-1543
Representative:	Erik Emerson, President and CEO
Telephone:	888-552-9796
Email:	emerson@symplmed.com

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Prestalia
- b) Non-Proprietary Name (USAN): perindopril arginine / amlodipine besylate
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

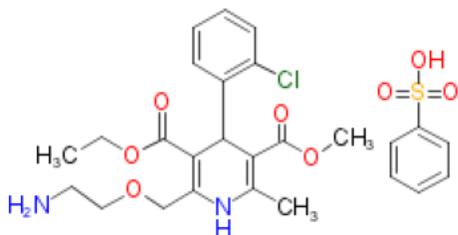
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) Aceon (NDA 20-184) and Norvasc (NDA 19-787)

10. PHARMACOL. CATEGORY: inhibitor of angiotensin-converting enzyme (perindopril) and calcium channel blocker (amlodipine)

## Chemistry Review Data Sheet

11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 3.5 mg / 2.5 mg; 7 mg / 5 mg; 14 mg / 10 mg
13. ROUTE OF ADMINISTRATION: oral
14. Rx/OTC DISPENSED:  Rx  OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)  
 SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



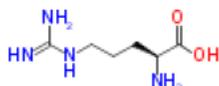
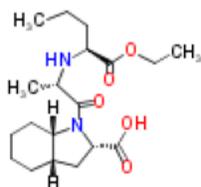
MW: 567.06 (salt form) or 408.15 (free base)

Molecular Formula:  $C_{20}H_{25}ClN_2O_5$ ,  $C_6H_6O_3S$

USAN Name: Amlodipine besylate

Chemical Name: 3-ethyl-5-methyl ( $\pm$ )-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate

Chemistry Review Data Sheet



MW: 542.67 (salt form) or 368.5 (free acid)

Molecular Formula: C<sub>19</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>, C<sub>6</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>

USAN Name: Perindopril Arginine

Chemical Name: L-arginine (2S,3aS,7aS)-1-N-[(S)-1-ethoxy-carbonyl butyl]-L-alanyl) perhydroindole-2-carboxylate

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II			1	Adequate	9/30/2014	2/24/2014 LOA
	II			1	Adequate	9/30/2014	2/3/2014 LOA references DMF (b) (4) as primary DMF
	II			1	Adequate	9/25/2014	1/8/2014 LOA
	III			4	Adequate	10/20/2014	12/21/2013 LOA
	III			4	Adequate	10/20/2014	12.12.2013 LOA
	III			4	Adequate	10/20/2014	12/6/2013 LOA
	III			4	Adequate	10/20/2014	12/6/2013 LOA
	III			4	Adequate	10/20/2014	12/6/2013 LOA
	III			4	Adequate	10/20/2014	12/6/2013 LOA

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	10/20/2014	12/6/2013 LOA
	III			4	Adequate	10/20/2014	12/6/2013 LOA
	III			4			1.21.2014 LOA
	III			4	Adequate	10/20/2014	1/31/2014 LOA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	108233	Pre-NDA Investigational drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		Jialu Zhang
EES	Pending		Vibhakar Shah
Pharm/Tox	Adequate	8/4/2014	Baichun Yang
Biopharm	Pending		Sandra Suarez
Pharmacovigilance	Pending		Amy Chen
Medication Errors	Pending, IR	7/16/2014	Janine Stewart
Methods Validation	Adequate	This Review	Charles Jewell
Marketing and Advertising Reviewer	Pending		Zarna Patel
EA	Adequate	9/30/2014	James Laurenson

## Chemistry Review Data Sheet

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Microbiology	Adequate	5/16/2014	Bryan Riley
Clinical	Pending		Karen Hicks
Clinical Pharmacology	Pending		Peter Hinderling
Labeling	Pending		Karen Dowdy
ONDQA RPM	Not applicable		Yvonne Knight
OND RPM	Not applicable		Wayne Amchin
Safety RPM	Not applicable		Lori Wachter

# The Chemistry Review for NDA 205003

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the CMC perspective, approval is recommended, pending an approval recommendation from the Biopharmaceutics reviewer and the CDER Office of Compliance. The (b) (4) manufacturing site (Amlodipine Besylate) and the Patheon manufacturing site (Drug Product) have an approval recommendation from the office of compliance. The (b) (4) manufacturing site (Perindopril arginine) is still awaiting the final inspection report and de n. The biopharmaceutics reviewer and clinical pharmacology review team is still determining whether there is an adequate bridge between the proposed drug product and the individual referenced monotherapy products. A formal bioequivalence study between the to-be-marketed fixed dose combination product and the mono-therapy reference products (ACEON® and NORVASC®) has been requested by an information request on 10/22/2014.

As of this review, labeling review has not been finalized.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

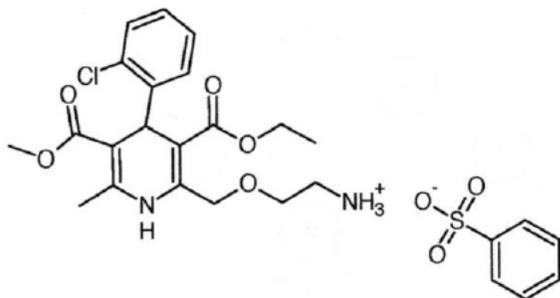
None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### a. Chemical Name or IUPAC Name/Structure

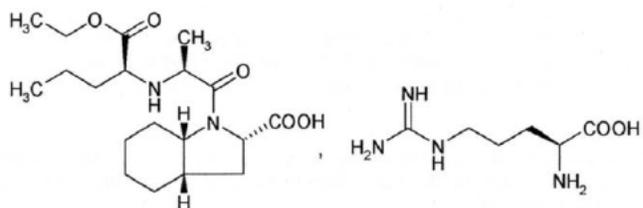
Amlodipine besylate is: 3-ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate



Perindopril arginine is:

(b) (4)

## Executive Summary Section



## b Properties/COAs Relevant to Drug Product Quality

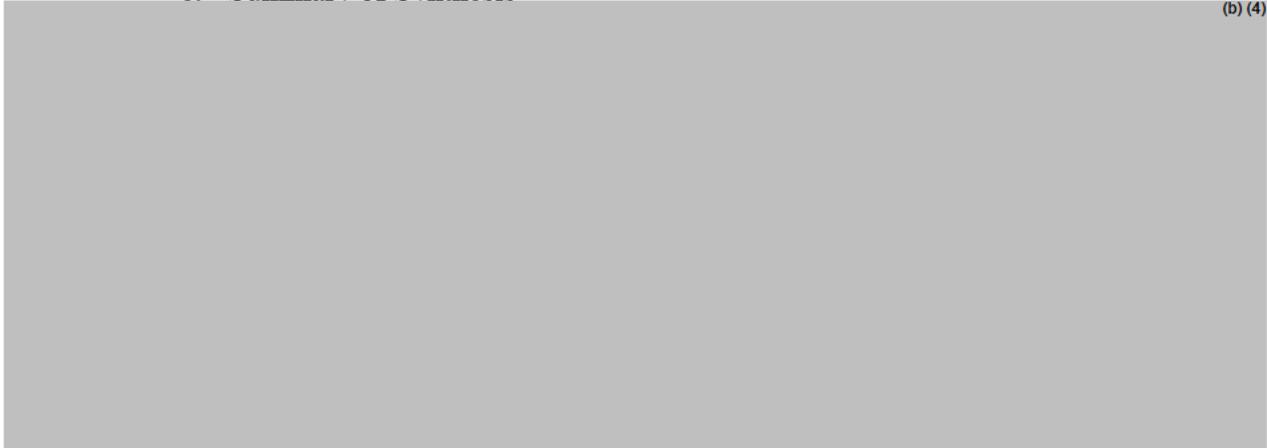
(b) (4)

(b) (4)

## Executive Summary Section

## e. Summary of Synthesis

(b) (4)



## f. Process

i.

(b) (4)

Not applicable.



(b) (4)

## g. Container Closure

(b) (4)



## h. Retest Period &amp; Storage Conditions

Amlodipine besylate: An <sup>(b)</sup><sub>(4)</sub> months retest period is supported based on long term (25°C / 60% RH) and accelerated (40°C / 75% RH) stability studies in the referenced DMF.

Perindopril arginine: Demonstrated stable for the following: 3 years at 25°C / 60% RH.; 1 year at 30°C / 65% RH; 6 months at 40°C / 75% RH

**B. Description of How the Drug Product is Intended to be Used**

## a. Strength

Three strengths are proposed, based on weight of perindopril arginine (an exception is allowed for this salt name) / and amlodipine (active moiety, when besylate salt is used):

## Executive Summary Section

- perindopril arginine 3.5 mg / amlodipine 2.5 mg
- perindopril arginine 7 mg / amlodipine 5 mg
- perindopril arginine 14 mg / amlodipine 10 mg

Note: The formulation for the three different strengths uses (b) (4). The 3.5/2.5 mg tablet weighs 52.0 mg; the 7/5 mg tablets weighs 104 mg and the 14/10 mg tablet weighs 208 mg. Total drug load is around 11.5%, not considering the besylate portion of the amlodipine besylate salt.

## b. Description/Commercial Image

Prestalia tablets are white, (b) (4) uncoated, designed as an immediate release solid oral dosage form.

- the 3.5/2.5 mg strength is debossed with 3.5 on one side and 2.5 on the opposite side
- the 7/5 mg strength is debossed with 7/5 on one side
- the 14/10 strength is debossed with 14/10 on one side

## c. Summary of Product Design

The product is formulated for immediate release.

The attributes of solubility, particle size distribution and polymorphism were considered with respect to **perindopril arginine** for this product. Solubility in water in the pH range of 1.0 to 9.0 is > 100 mg/mL. Particle size distribution did not seem to be pertinent, (b) (4)

(b) (4)  
Due to the high solubility of all polymorphs, this was not considered a critical attribute.

The same attributes as above were also considered with respect to amlodipine besylate. Water solubility is 10 g/100 mL. Particle size was found not to be pertinent (b) (4)

(b) (4)  
Both drug substances were demonstrated compatible with each other with regard to decomposition under stressed conditions (temperature and humidity). They were also demonstrated stable under temperature stress with individual components.

## d. List of Excipients:

Lactose (b) (4), magnesium stearate, microcrystalline cellulose and colloidal silicon dioxide.

## e. Process Selection (Unit Ops Summary)

(b) (4)

## Executive Summary Section

(b) (4)

i. Sterilization processes of the drug product, as applicable  
Not applicable.

ii. Critical equipment

(b) (4)

f. Container Closure

The drug product is packaged into a 90-count HDPE bottle (100 mL, (b) (4) white, round, wide mouth) (b) (4) (b) (4) induction seal) and induction seal.

g. Expiration Date & Storage Conditions

- 3.5 mg / 2.5 mg strength: 18 months
- 7 mg / 5 mg strength: 24 months
- 14 mg / 10 mg strength: 24 months

Note: The most prominent degradation products are (b) (4) (b) (4) (b) (4) *in vivo* metabolite), (b) (4) and (b) (4) (b) (4). These are adequately qualified at their specified limits.

h. List of co-packaged components

- polyester coil filler
- 1 g silica gel canister

### C. Basis for Approvability or Not-Approval Recommendation

The potential critical attributes for this drug product are its stability, solubility differences between potential polymorphic changes in drug substance solid forms, the content uniformity due to the medium drug loading for this product, dissolution and microbial limits. These attributes are adequately controlled due to adequate in-process testing and release controls. These controls have been developed with adequate process understanding and manufacturing experience. The risk of inadequate performing drug product is considered low. The product manufacturing process is consistent due to the controls over the potential critical attributes.

## Executive Summary Section

From Initial Quality Assessment			Review Assessment		
Product attribute/CQA	Factors that can impact the CQA	Risk Ranking* (H, M, L)	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/Comments**
Assay, Stability	Degradation - hydrolytic and photolytic (amlodipine)	L	Container closure affords light protection; HDPE bottles contain desiccant.	L	Due to potential light mediated instability of amlodipine, ensure all containers offer appropriate protection from light exposure.
Physical Stability (solid state)	Particle size; polymorph inter conversion	L	Only one morphic form of amlodipine known. Stable form of perindopril is understood and controlled. (b) (4)	L	Because of high solubility of both components, the risk of solid state issues is extremely low.
Content Uniformity	(b) (4)	M	controlled by adequate sampling prior to direct compression to tablets	L	Make sure process changes include appropriate (b) (4) monitoring.
Microbial Limits	Segregation Moisture; equipment; process; environment	L	Microbiology review found adequate	L	This product has an extremely low risk of microbial contamination based on original manufacturing practice. For most oral dosage forms the risk will remain low.
Dissolution BCS Class 1 and 3	Particle size; moisture; Tablet hardness; disintegration	L	both drug substances are highly water soluble at wide pH range. Only at extremely high pH is hydrolysis a problem.	L	Dissolution occurs rapidly with these drug substances manufactured in immediate release form so risk is low. This should carry over into other immediate release forms. In changing to an extended release form, dissolution will become a higher risk factor.

\* Risk ranking applies to product attribute/CQA

\*\* For example, post marketing commitment, knowledge management post approval, etc.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

**C. CC Block**

92 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

## Chemistry Assessment Section

**Signatures:**

Charles Jewell -S

Digitally signed by Charles Jewell -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
cn=Charles Jewell -S, 0.9.2342.19200300.100.1.1=2000403529  
Date: 2014.11.14 09:09:26 -05'00'

Olen Stephens -S

Digitally signed by Olen Stephens -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S,  
0.9.2342.19200300.100.1.1=2000558826  
Date: 2014.11.14 09:23:33 -05'00'

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlopidine FDC Tablet**

## IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205003

2. DATES AND GOALS:

Letter Date: Mar. 21, 2014	Submission Received Date : Mar. 21, 2014
PDUFA Goal Date:	Jan. 21, 2015

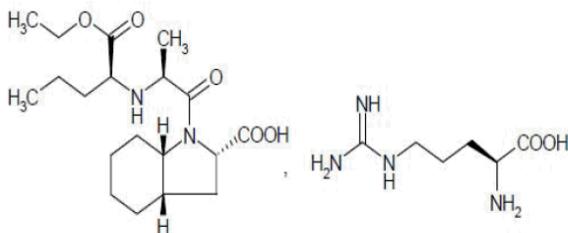
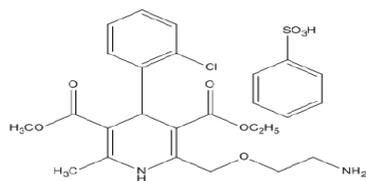
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Prestalia (proposed)
Established or Non-Proprietary Name (USAN):	Perindopril arginine and amlodipine
Dosage Form:	Tablets
Route of Administration	Oral
Strength/Potency	3.5/2.5 mg, 7/5 mg and 14/10 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: Hypertension

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

### Amlodipine Besylate



### Perindopril arginine

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

6. NAME OF APPLICANT (as indicated on Form 356h): Symplmed Pharmaceuticals LLC

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 4
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Cardiovascular and Renal Products

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment	X		
CDRH		X	
Other	X		Microbiology

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlopidine FDC Tablet**

## Overall Filing Conclusions and Recommendations

### CMC:

<b>Is the Product Quality Section of the application fileable from a CMC perspective?</b> Yes
CMC Filing Issues: None

<b>Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?</b> Yes
CMC Comments for 74-Day Letter: Section 3.2.S. is incomplete and 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 DMFs, where appropriate, for additional details.

### Biopharmaceutics:

<b>Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?</b> Yes
<b>Biopharmaceutics Filing Issues:</b> None

<b>Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?</b> Yes
<b>Biopharmaceutics Comments for 74-Day Letter:</b> Submit the following information: <ol style="list-style-type: none"><li>1. Include the solubility profile in the physiologically relevant pH for both components.</li><li>2. 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.</li><li>3. A list of the critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution with supporting data.</li><li>4. Dissolution data for both components supporting the discriminating ability of the dissolution method towards the CMAs and/or CPPs.</li></ol> 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.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

**Microbiology:**

**Is the Product Quality Section of the application fileable from a Microbiology perspective?**

Yes

Kasturi,

This submission is acceptable from a product quality microbiology standpoint and will be recommended for approval. Therefore, no product quality microbiology reviewer assignment will be made for this submission. A review memo describing the assessment of the microbial controls for the drug product will be entered into DARRTS.

Thanks,  
Bryan

**Bryan S. Riley, Ph.D.**  
Team Leader (Acting)  
New Drug Microbiology Staff  
CDER/OPS  
U.S. Food and Drug Administration

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlopidine FDC Tablet**

## Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	

Is a team review recommended?	No
Suggested expertise for team: No special expertise required. DMF references are provided for both drug substances which have to be reviewed. Simple formulation and manufacturing process.	

### Summary of Critical Issues and Complexities

**Drug Substance:**

- Both Type II DMFs, (b)(4) for perindopril arginine and amlodipine besylate respectively, are new and have never been reviewed. These will need a comprehensive evaluation.
- The Module 3 Drug Substance section is incomplete with information provided only for 3.2.S.4. Although most of the information can be cross-referenced to DMFs, basic aspects like physico-chemical properties, structure etc. should be included along with a discussion of those attributes that are critical to manufacture and stability of the drug product.
- Has the starting material issue, in the amlodipine besylate synthesis, discussed at a meeting with the Applicant, been resolved by the DMF holder?
- Are the proposed particle size acceptance criteria for both amlodipine besylate and perindopril arginine justified?

**Drug Product:**

- Has the compatibility of the drug substances with each other and with the excipients been adequately demonstrated?
- Is the manufacturing process described in satisfactory detail with appropriate in-process controls? In lieu of a Master Batch Record is there a statement that the process described in the Executed Batch Records will be followed for the commercial batches?
- How is blend uniformity established for the commercial process?
- The specifications do not include quantification of (b)(4) as recommended in the pre-NDA meeting. Has the Applicant provided a satisfactory justification for this omission?
- Impurities (b)(4) have acceptance criteria above the qualification threshold in the drug product specification. Pharm/tox should be consulted to verify that these degradation products are qualified by toxicity studies as claimed.
- Why is a shelf-life of only (b)(4) months claimed for the lowest strength, in contrast to the 24 month shelf-life proposed for the other 2 strengths?

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
**CMC and Biopharmaceutics**  
**NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

- Regarding Labeling—
  - Both container labels and the PI need to be revised since the strength of amlodipine corresponds to the free base and not the salt, amlodipine besylate. An equivalency statement should also be included separately on the container labels.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlopidine FDC Tablet**

## Initial Quality Assessment

This is a 505(b)(2) application for a fixed dose combination (FDC) drug product of perindopril arginine and amlodipine besylate. Both perindopril (tradename Aceon) and amlodipine (tradename Norvasc) are previously approved drugs under NDAs 20184 and 19787 respectively and this application relies on the Agency's finding of safety and efficacy of these individual drugs. Perindopril was approved as the erbumine (t-butylamine) salt whereas in this application the arginine salt form, approved in the EU, is used. A Phase 3 study was carried out under IND 108233, in support of this NDA, comparing the highest strength of the FDC with the highest strengths of the individual components administered as monotherapies.

Three meetings have been held with the Applicant starting with the pre-IND meeting on Oct. 20, 2010. The main CMC issues discussed were the proposed starting material for the synthesis of amlodipine besylate, which the Agency considered unacceptable due to its proximity to the drug substance, specifications for the drug substance and the stability data package for the drug product expected at the time the NDA is submitted. The second meeting scheduled for Nov. 15, 2012 to discuss biowaivers was cancelled based on the written responses sent to the Applicant. The third meeting, held on Nov. 4, 2013, was a pre-NDA meeting and included several CMC topics. The Agency indicated that the (b) (4), should be identified and quantified in the (b) (4) specifications but the Applicant presented a lengthy argument why they did not consider this necessary. In the end, the Agency agreed with their justification. A similar case was made by the Applicant for the (b) (4) in amlodipine besylate. However, for the drug product the Applicant was told that it would be necessary to quantify levels of (b) (4) in release testing to establish that these were not altered or degraded during product manufacture. Alternatively, demonstration through compatibility studies under standard manufacturing conditions that no degradation or decrease in salt concentration took place could be acceptable in lieu of release testing. The labeling of perindopril arginine strengths in terms of the salt instead of the free base, in contradiction to current USP policy, was accepted since the strengths of the marketed product, Aceon, are also expressed as the salt.

**Drug Substance:** Perindopril arginine is a white to almost white powder which is freely soluble in water, sparingly soluble in alcohol and almost insoluble in methylene chloride. Perindopril free acid has 5 stereogenic centers and is synthesized as a single enantiomer. (b) (4)

(b) (4) It is stated that a single morphic form is obtained by the synthetic route and that this is the most stable form under ambient conditions. All CMC information for this drug substance is by reference to DMF (b) (4). The NDA contains specifications, analytical methods and batch analysis data for perindopril arginine. Batch data are provided for perindopril arginine used in non-clinical studies and manufacture of clinical and registration product lots.

Amlodipine besylate is a white to almost white powder which is synthesized as a racemic mixture. Its solubility in water is 10 g/100 mL whereas in methanol it is <0.1g/100mL. It is claimed that only one crystalline form is produced by the synthetic route and that only one form has been reported in the literature. CMC information for amlodipine besylate is provided in

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
**CMC and Biopharmaceutics**  
**NDA 205-003, perindopril arginine/amlopidine FDC Tablet**

DMF (b) (4). The NDA contains specifications, analytical methods and batch analysis data for amlodipine besylate. Batch data are provided for amlodipine besylate used in non-clinical studies and manufacture of clinical and registration product lots.

**Drug Product:** Three strengths of the combination drug product are proposed for marketing, 3.5 mg/2.5 mg, 7 mg/5 mg and 14 mg/10 mg where the first number refers to perindopril arginine expressed as the salt and the second number refers to amlodipine free base. The dosage form is immediate release, white, uncoated tablets. This combination is marketed in the EU but in different strengths: (b) (4)

Although the strengths currently marketed OUS are different from those proposed for the US market, the same actives and inactive ingredients are used in both. The US marketed perindopril monotherapy product, ACEON, is the erbumine (t-butylamine) salt whereas the proposed FDC will contain perindopril arginine. Standard compendial excipients are used in the proposed formulation: lactose (b) (4) microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate. Since a similar product is currently marketed outside the US, the Applicant has used prior knowledge in both formulation and process development. QbD elements are absent in the submission. There is no difference between the formulation used to manufacture the 14/10 mg product for the clinical study, the registration stability batches and the proposed commercial product. However, there is a slight difference between the Servier formulation (EU) and the XOMA 985 formulation (US) – magnesium stearate concentration is increased from (b) (4) % in the Servier formulation to (b) (4) % in the XOMA 985 formulation with corresponding adjustments to lactose (b) (4) concentration. The arginine salt of perindopril was chosen because of its enhanced stability to elevated temperatures and humidity.

The prior experience with the commercial product manufacturing process at Servier was leveraged in the transfer to Patheon for the manufacture of XOMA 985 tablets for the intended US market. (b) (4) (b) (4)

(b) (4)

(b) (4) (b) (4)

(b) (4)

Specifications for the drug product are proposed with the standard test attributes of appearance, identification, assay, degradation products, uniformity of dosage units, dissolution and microbiological quality. A number of degradation products are specified with acceptance criteria ranging from  $\leq$  (b) (4) % to  $\leq$  (b) (4) %. Three of the degradation products exceed the qualification threshold of (b) (4) %. Structures of all 8 degradation products are given. Dissolution acceptance

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
**CMC and Biopharmaceutics**  
**NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

criteria are  $Q = \frac{(b)}{(4)}\%$  at 15 min for both drug components using Apparatus 2. Analytical results from registration batches, clinical batches and batches used in generating dissolution profiles to support the biowaiver requests have been submitted. The registration batches and clinical batches were manufactured at the intended commercial site and scale. Stability studies have been carried out on the registration batches of XOMA 985 tablets using three batches each of the lowest and highest strengths and one batch of the middle strength. The Applicant states that the bracketing strategy was justified based on the use of a (b) (4) for compression. The batches were manufactured at commercial scale at the intended commercial site and packaged in 90-count HDPE bottles with desiccant and filler and a (b) (4) closure and induction seal. This is the container closure proposed for marketing. 12 months of long term data (25°C /60% RH) and 6 months of accelerated data (40°C/75% RH) are provided. The attributes tested include appearance, assay, degradation products, water content, dissolution and microbiological quality. Supportive data on a batch of the 14/10 mg strength used in Phase 1/3 clinical studies are also available. A shelf-life of 24 months is proposed for the 7/5 mg and 14/10 mg strengths whereas a (b) (4) month shelf-life is proposed for the lowest strength, 3.5/2.5 mg, of XOMA 985 tablets.

**Additional Comments:** Facilities for inspection have been entered in the EES database. Methods validation will not be requested at this time since this is not an NME. An Environmental Assessment report has been submitted and a consult request will be sent to the EA staff to review this section.

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
**CMC and Biopharmaceutics**  
**NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

**Biopharmaceutics Critical Issues or Complexities**

**Submission:** Symplmed is seeking approval of Xoma 985 Tablets, a fixed-dose combination of perindopril arginine and amlodipine in doses of 3.5/2.5 mg, 7/5 mg, and 14/10 mg for the treatment of hypertension. This is a 505(b)(2) application, which relies upon data from a Phase 3 clinical study (X985400 [PATH]) comparing the highest strength of the combination product to those of the highest strength of the individual components administered as monotherapies, a Phase 2 study (CL2-05985-005) comparing the effects of the lowest strength of the combination product with those of the individual components administered as monotherapies, and results from the Agency's previous findings of safety and efficacy of the individual drugs ACEON® (perindopril erbumine, NDA 020184) and NORVASC® (amlodipine, NDA 019787).

**Biopharmaceutics Issues:** As part of this 505(b)(2) application, a request for biowaivers is included as follows:

1. A biowaiver for a comparative bioavailability study for a 505(b)(2) NDA;  
According to the Applicant, this is a different dose compared with the approved drug product for 8 mg perindopril terbumine per tablet (currently in US market [NDA 20-184, Aceon®]), but the same dose for amlodipine (currently approved amlodipine 10 mg per tablet [NDA 19-787]).
  - a. A cross-study comparison of the bioavailability information based on the food-effect pharmacokinetic (PK) study of XOMA 985 FDC (14/10 mg) (Protocol X985401) and publicly available PK data for Aceon and Norvasc is included. This BA data will be reviewed by OCP.
    - During the IND stage it was concluded that since the sponsor is conducting a phase 3 efficacy/ safety trial and a food effect study with cross-study PK analysis, the proposed data/information were sufficient to establish a bridge.
2. A biowaiver for a bioequivalence study to bridge the clinical studies conducted by Servier outside the United States (US) and the clinical studies conducted by XOMA in the US due to different manufacturers. The data supporting this biowaiver are as follows:
  - a. Side-by-side comparison of the component and composition of the products manufactured at the two sites.
  - b. Dissolution profile comparisons in three different media for the three strengths.
  - c. Information on the comparative of the manufacturing process
3. A biowaiver for a dosage form equivalence study. The data included to support the waiver for the lower strengths are as follows:
  - a. Components and composition;
  - b. Manufacturing process
  - a. Dissolution profile comparison with similarity testing in three different media using a paddle apparatus (1000 mL, 37 ± 0.5°C, 75 rpm)

**Review:** The biopharmaceutics review will focus on the acceptability of the data provided to support the dissolution method and, approval of the lower strengths (3.5/2.5 mg, 7/5 mg), and

**ONDQA Initial Quality Assessment (IQA) and Filing Review**  
**CMC and Biopharmaceutics**  
**NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

that appropriate data has been provided to support the approval of the different manufacturing sites.

**Review Issues Identified:**

1. The dissolution profile comparisons conducted to support the approval of the lower strengths failed the similarity criteria (e.g. (b) (4)), suggesting lack of dose-proportionality; therefore, the clinical relevance of this findings needs to be discussed with the clinical review team.
2. The dissolution profile comparisons conducted to support the bridge between the clinical studies conducted by Servier outside the United States (US) and the clinical studies conducted by XOMA in the US failed the similarity criteria (b) (4) in some media (pH 6.8); however all the batches dissolved more than (b) (4)% in 15 min. The clinical relevance of fast dissolving batches will be evaluated.

**Recommendation:** The NDA is fileable from biopharmaceutics perspective. There are information request comments to be included in the 74-Day letter (refer to page 3 of this document).

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

## FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
<b>* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.</b>				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Incomplete list in the original submission but later amended in response to our request
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlo地平ine FDC Tablet**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		Amendment dated 04-08-2014
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		Environmental assessment submitted. Consult will be requested from EA staff.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMFs (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Cross-reference to DMFs (b) (4)
14.	Does the section contain information regarding the characterization of the DS?			Cross-reference to DMFs (b) (4)
15.	Does the section contain controls for the DS?			Cross-reference to DMFs (b) (4)
16.	Has stability data and analysis been provided for the drug substance?			Cross-reference to DMFs (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		No master batch record
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlo地平ine FDC Tablet**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		See table below

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	2-24-2014	
	II		1-8-2014		
	III		12-21-2013		
	III		12-12-2013		
	III		12-6-2013		
	III		12-6-2013		
	III		1-31-2014		
	III		1-21-2014		
	III		12-6-2013		
			12-6-2013		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

(b) (4)	III	(b) (4)	12-6-2013	
	III		12-6-2013	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	x		<p><b>Proposed dissolution method for both components:</b> USP 2, 75 rpm, 1000 mL of 0.01N HCl pH 2 at 37°C.</p> <p>Refer to section 3.2.2.3 <a href="#">(\\cdsub1\evsprod\NDA205003\0000\m3\32-body-data\32p-drug-prod\perindopril-arginine-amlodipine-besylate\32p2-pharm-dev)</a></p>
35.	Is the dissolution test part of the DP specifications?	x		<p>Proposed dissolution acceptance criteria: Q= (b) (4) at 15 min for both components</p> <p>Refer to: <a href="#">\\cdsub1\evsprod\NDA205003\0000\m3\32-body-data\32p-drug-prod\perindopril-arginine-amlodipine-besylate\32p5-contr-drug-prod\32p56-justif-spec</a></p>

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlo地平ine FDC Tablet**

36.	Does the application contain the dissolution method development report including data supporting the discriminating ability?	x		Discriminating ability was evaluated towards differences in hardness.  Refer to:  <a href="\\cdsesub1\evsprod\NDA205003\0000\m3\32-body-data\32p-drug-prod\perindopril-arginine-amlo地平ine-besylate\32p2-pharm-dev">\\cdsesub1\evsprod\NDA205003\0000\m3\32-body-data\32p-drug-prod\perindopril-arginine-amlo地平ine-besylate\32p2-pharm-dev</a>
37.	Is there a validation package for the analytical method and dissolution methodology?	x		This data will be review by the CMC reviewer.
38.	Does the application include a biowaiver request?	x		This is a 505 (b)(2) application which includes 3 biowaiver requests: 1. A biowaiver for a comparative bioavailability study for a 505(b)(2) NDA; 2. A biowaiver for a bioequivalence study to bridge the clinical studies conducted by Servier outside the United States (US) and the clinical studies conducted by XOMA in the US due to different manufacturers. 3. A biowaiver for a dosage form equivalence study.  <a href="\\cdsesub1\evsprod\NDA205003\0000\m1\us">\\cdsesub1\evsprod\NDA205003\0000\m1\us</a>
39.	Is there information/data supporting the biowaiver request?	x		Refer to : <a href="\\cdsesub1\evsprod\NDA205003\0000\m2\27-clin-sum">\\cdsesub1\evsprod\NDA205003\0000\m2\27-clin-sum</a>
40.	Is there enough information to assess the extended release designation claim?		x	Not applicable
41.	Are there data available to support the approval of the lower strengths?	x		Three strengths are being proposed: 3.5/2.5 mg, 7/5 mg, and 14/10 mg. Refer to the following link for the data submitted to support the approval of these strengths: <a href="\\CDSESUB1\evsprod\NDA205003\0000\m2\27-clin-sum">\\CDSESUB1\evsprod\NDA205003\0000\m2\27-clin-sum</a>

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlo地平ine FDC Tablet**

42.	Are there any manufacturing changes implemented to the biobatch/clinical trial formulation?	x		<p>A biowaiver for a bioequivalence study to bridge the clinical studies conducted by Servier outside the United States (US) and the clinical studies conducted by XOMA in the US due to different manufacturers. The data supporting this biowaiver are as follows:</p> <ol style="list-style-type: none"> <li>a. Side-by-side comparison of the component and composition of the products manufactured at the two sites.</li> <li>b. Dissolution profile comparisons in three different media for the three strengths.</li> <li>c. Information on the comparative of the manufacturing process</li> </ol> <p>Refer to:</p> <p><a href="\\CDSESUB1\evsprod\NDA205003\0000\m2\27-clin-sum">\\CDSESUB1\evsprod\NDA205003\0000\m2\27-clin-sum</a></p>
43.	Are data supporting the manufacturing changes implemented to the clinical trial formulation?			See 43.
44.	Does the application include an IVIVC model?		x	
45.	Does the application include information/data on in vitro alcohol dose-dumping potential?		x	Not Applicable
46.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		<p>Three clinical pharmacology studies in healthy volunteers were included in this submission:</p> <ul style="list-style-type: none"> <li>• a single dose comparative bioequivalence study (PKH-05985-001),</li> <li>• a drug interaction study between PERa and AML (PKH-05985-009), and</li> <li>• a food effect study (X985401)</li> </ul> <p>These studies will be reviewed by OCP.</p>

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlo地平ine FDC Tablet**

47.	Is there any design space proposed using in vitro release as a response variable?		x	
48	Is the control strategy related to in vitro drug release?		x	
<b>K. filing conclusion</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
49.	<b>IS BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		<ul style="list-style-type: none"> <li>• The NDA is fileable from the Biopharmaceutics Perspective</li> <li>• The acceptability of dissolution method and acceptance criterion will be a review issue.</li> <li>• The adequacy of the data supporting the manufacturing sites will be a review issue.</li> <li>• The data supporting the approval of the lower strengths will be a review issue</li> </ul>
51	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons.			Not applicable.
52	Are there any potential review issues identified?		x	<ol style="list-style-type: none"> <li>1. The dissolution profile comparisons conducted to support the approval of the lower strengths failed the similarity criteria (e.g. (b)(4) suggesting lack of dose-proportionality; therefore, the clinical relevance of this findings needs to be discussed with the clinical review team.</li> <li>2. The dissolution profile comparisons conducted to support the bridge between the clinical studies conducted by Servier outside the United States (US) and the clinical studies conducted by XOMA in the US failed the similarity criteria (e.g. (b)(4) in pH 6.8 medium; however all the batches dissolved more than (b)(4)% in 15 min. The clinical relevance of fast dissolving batches will be evaluated.</li> </ol>

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

53	Are there any comments to be sent to the Applicant?	x		There are biopharmaceutics information request comments to be conveyed to the Applicant in the 74-Day letter. Refer to page 3.
54.	Are there any internal comment to other disciplines:		x	

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
CMC and Biopharmaceutics  
NDA 205-003, perindopril arginine/amlodipine FDC Tablet**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

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