

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205003Orig1s000

Trade Name: Prestalia

Generic Name: Amlodipine besylate; Perindopril arginine

Sponsor: Symplmed Pharms LLC

Approval Date: January 21, 2015

Indications: 1) For the treatment of hypertension, to lower blood pressure. Prestalia may be used in patients whose blood pressure is not adequately controlled on monotherapy. Prestalia may be used as initial therapy if a patient is likely to need multiple drugs to achieve their blood pressure goals.

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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 205003

NDA APPROVAL

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 and amlodipine) 3.5/2.5 mg, 7/5 mg, and 14/10 mg tablets.

We acknowledge receipt of your amendments dated April 4, 8, 25, May 5, 6, 15, June 18, 27, July 3, 8, 25, August 5, 6, 14, 18, 25, September 3, 12, 17, 18, 23, October 9, 14, 16, 31, November 20, 21, 24 (2), 25, 26, December 10 (2), 19 (2), 22, 2014, and January 15, 16, and 20, 2015.

This new drug application provides for the use of Prestalia (perindopril arginine and amlodipine) tablets for the treatment of hypertension, to lower blood pressure. Prestalia may be used in patients whose blood pressure is not adequately controlled on monotherapy. Prestalia may be used as initial therapy if a patient is likely to need multiple drugs to achieve their blood pressure goals.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on December 19, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 205003.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

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 are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of excessive hypotension, acute renal failure, and clinically significant hyperkalemia as a result of increased exposure to perindopril in the elderly (age >65 years), or in patients with heart failure, renal impairment (creatinine clearance <60 mL/min) or hepatic impairment. The pivotal trial for Prestalia (perindopril arginine and amlodipine) did not enroll these patient subgroups. Moreover, according to the approved label for ACEON (perindopril erbumine), there is increased exposure to perindopril in these patient subgroups warranting dose adjustment of ACEON. Because we do not have a clear understanding of the relative bioavailability between Prestalia

(perindopril arginine and amlodipine) and ACEON (perindopril erbumine), we are unable to provide dosing recommendations for these subgroups for Prestalia (perindopril arginine and amlodipine).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these known serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2858-1 A bioequivalence trial of Prestalia (perindopril and amlodipine) and ACEON (perindopril erbumine) in healthy volunteers. The proposed trial will provide an accurate estimate of the relative bioavailability of perindopril and the active metabolite perindoprilat to enable appropriate dosing instructions for elderly (age > 65) patients, or for patients with heart failure, renal impairment (creatinine clearance < 60 mL/min), or hepatic impairment.

The timetable you submitted on January 12, 2015, via email states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/15
Trial Completion:	02/16
Final Report Submission:	06/16

Submit the protocols to your IND 108233, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o)

on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Enclosure(s):

Content of Labeling
Carton and Container Labeling

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
01/21/2015