DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205920

NDA APPROVAL

Armstrong Pharmaceuticals, Inc.
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs
11570 6th Street
Rancho Cucamonga, CA 91730

Dear Ms. Sharp:

Please refer to your new drug application (NDA) dated July 22, 2013, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Primatene Mist (epinephrine) inhalation aerosol, 125 mcg per spray.

We acknowledge receipt of your amendment dated May 5, 2018 and received May 7, 2018, which constituted a complete response to our December 23, 2016, action letter.

This new drug application provides for the over-the-counter use of Primatene Mist (epinephrine) inhalation aerosol, 125 mcg per spray for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

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 agreed-upon labeling text.

LABELING

Submit final printed labeling (FPL), as soon as they are available, but no more than 30 days after they are printed. The final printed labeling must be in the "Drug Facts" format (21 CFR 201.66), where applicable, and be identical to the following:

Submitted Labeling	Date submitted via email
160-spray, 11.7 g outer container label	October 25, 2018
160-spray, 11.7 g immediate container label	October 9, 2018
Actuator label	October 9, 2018
Consumer information insert	October 9, 2018

The final printed labeling should be submitted electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4)*. For administrative purposes, designate this submission "**Final Printed Labeling for approved NDA 205920**." Approval of this submission by FDA is not required before the labeling is used.

ADDITIONAL COMMENTS

1. Approval of this NDA includes a single immediate container with 160 metered sprays. Limiting package sizes has been shown to reduce overconsumption by limiting the immediate availability of drugs to the consumer.[1,2] In addition, during the 2014 Joint meeting of the Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committee to discuss epinephrine inhalation aerosol for over-the-counter use, several members suggested that a high number of actuations per inhaler could encourage chronic use and delay health care provider visits, which would raise additional safety concerns.[3]

   We remind you that, if you are interested in marketing other configurations in the future (e.g., immediate containers containing greater than 160 metered sprays, package sizes with more than one inhaler), we expect submission of a prior approval supplement that includes clinical data to justify why larger pack sizes will not adversely impact the safety of the product. Consider requesting a meeting with us prior to submission of such a supplement, to discuss safety implications and your proposed justification to support a larger package configuration.

2. We acknowledge your submission dated October 11, 2018, which states that you will use epinephrine batches from [redacted] (b) (4) for production of drug product, and [redacted] (b) (4) remains your commercial supplier until 2019. In addition, we acknowledge your commitment to [redacted] (b) (4) after approval of this NDA.

[1] Hawton K, H Bergen, S Simkin, S Dodd, P Pocock, W Bernal, et al., 2013, Long Term Effect of Reduced Pack Sizes of Paracetamol on Poisoning Deaths and Liver Transplant Activity in England and Wales: Interrupted Time Series Analyses, *BMJ*, 346: f403 (doi: 10.1136/bmj f403).
[2] Weiss S, 2009, Compliance Packaging for Over-the-counter Drug Products, J Public Health, 17(2): 155-164.
[3] The details and links to the advisory committee briefing material including the meeting minutes and transcript may be accessed at the archived webpage http://wayback.archive-it.org/7993/20170111194827/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm380890 htm under the section February 25, 2014 Meeting of the Nonprescription Drugs Advisory Committee (accessed October 18, 2018).

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for children under four years of age because necessary studies are impossible or highly impracticable. Children in this age group have not yet developed the dexterity and coordination of efforts to adequately use the device for its intended purpose. Additionally, national guidelines, particularly the National Asthma Education and Prevention Program (NAEPP, NIH), indicate that asthma is difficult to diagnose in children under four years.

We are deferring submission of your pediatric study for ages 4 to 11 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

3514-1 Multiple dose safety and efficacy trial with three arms in 4 to 11 year old pediatric subjects with asthma comparing a two-inhalation dose of the test product epinephrine inhalation metered dose inhaler (125 mcg/inhalation), a one-inhalation dose of the test product, and placebo. The trial must include an assessment of epinephrine exposure around T_{max} for both epinephrine arms in the safety and efficacy trial.

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2019
Study/Trial Completion:	05/2020
Final Report Submission:	08/2020

Submit the protocol(s) to your IND 74286, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that you have fulfilled the pediatric study requirement for ages 12 to 17 years for this application.

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, call Helen Lee, Regulatory Project Manager, at (301) 796-6848.

Sincerely,

{See appended electronic signature page}

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE(S):
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA M MICHELE
11/07/2018