CLINICAL REVIEW

Application Type	NDA 505(b)(2); SDN – 73 Class 2 Resubmission Second Resubmission – Response to Complete Response Letter
Application Number(s)	205920
Priority or Standard	Standard
Submit Date(s)	May 5, 2018
Received Date(s)	May 7, 2018
PDUFA Goal Date	November 7, 2018
Division/Office	Division of Nonprescription Drug Products (DNDP)/ODE IV
Reviewer Name(s)	Suhail Kasim, MD MPH
Review Completion Date	October 14, 2018
Established/Proper Name	Epinephrine Inhalation Aerosol
(Proposed) Trade Name	Primatene Mist
Applicant	Armstrong Pharmaceuticals, Inc.
Dosage Form(s)/ Route of Administration / Strength	Aerosol, metered / Inhalation (metered dose inhaler (MDI)/ 125 mcg per actuation
Applicant Proposed Dosing Regimen(s)	1-2 inhalations every 4 hours as needed maximum 8 inhalations in 24 hours
Applicant Proposed Indication(s)/Population(s)	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Recommendation on Regulatory Action	Approval

Reference ID: 4338147

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CIL	Consumer instructions for use Information Leaflet
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DFL	Drug Facts Label
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

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NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1. Executive Summary

1.1. Product Introduction

Armstrong Pharmaceuticals, Inc. (Armstrong) resubmitted the NDA 505(b)(2) supplement on May 7, 2018 for the third cycle review (second resubmission) seeking approval for epinephrine inhalation aerosol, using hydrofluoroalkane propellant in the single-ingredient drug-device combination metered dose inhaler product (hereafter referred to as epinephrine HFA) at a dose of 125 mcg per actuation for nonprescription use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

During the epinephrine HFA development program, the product was referred to as E004. Primatene Mist is the proposed proprietary trade name.

A chlorofluorocarbon based Primatene Mist epinephrine metered dose inhaler (hereafter referred to as epinephrine CFC) was previously marketed, although it was withdrawn from distribution in 2011 when metered dose inhalers using ozone-depleting chlorofluorocarbon (CFC) propellants began to be phased out in 1996 in compliance with the Montreal Protocol. The epinephrine CFC metered dose inhaler was approved for nonprescription use for the treatment of symptoms of asthma on November 8, 1967 under NDA 016126. The previously marketed Primatene Mist epinephrine CFC metered dose inhaler was not discontinued due to reasons of safety.

This NDA 205920 supplement class 2 resubmission included Armstrong's complete response to deficiencies identified during the second cycle review and outlined in the letter dated December 23, 2016. An overview of the complete response and relevant discussions supporting the recommendations in the benefit-risk discussion for the epinephrine HFA nonprescription product are included in section 8.1 as they pertained to minimizing clinically important use errors that could result in superpotent dose or overdosing and subpotent dosing. Since there were no clinical trial data submitted to this third cycle NDA 205920 resubmission, this document provides a brief update of regulatory activities since the second cycle complete response, recommendations for the proposed labeling with supporting information, and information about required postmarketing pediatric studies under PREA. Previously reviewed clinical information to determine safety and efficacy will not be repeated in this document, and will include references to the information previously reviewed. Numbering for this review follows the clinical template, but missing headers are purposeful and not relevant to this review.

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1.2. Conclusions on the Substantial Evidence of Effectiveness

Clinical efficacy trials reviewed during the first review cycle demonstrated bronchodilator efficacy of epinephrine HFA compared to placebo for the primary endpoint for the proposed 125 mcg per actuation, and the efficacy results were also comparable to those observed with epinephrine CFC product. Effectiveness, i.e., whether the efficacy of the epinephrine HFA product is generalizable to nonprescription product consumers in 'real world' use, was assessed in the previously conducted label comprehension studies of consumer behavior, and in the behavioral human factors study.

Previous NDA 205920 submissions reviewed to support epinephrine HFA marketing discussed the objectives for the development program for epinephrine HFA and that it was designed to focus only on elements that differed from the previously available epinephrine CFC product label, and did not focus on self-selection or safety questions related to the label that are commonly evaluated as part of a de novo nonprescription product development program. Please see discussion of summary product characteristic differences between the epinephrine CFC metered dose inhaler compared to the currently proposed epinephrine HFA product in section 2, and Table 1.

Considering the above-mentioned objectives, the Division of Nonprescription Drug Products considered information obtained from human factors validation studies to be reflective of epinephrine HFA product use in the nonprescription setting. Consumers rely on the labeled packaging instructions without the intervention of healthcare provider/learned intermediary. Human factors studies are part of an iterative design process that is driven by the complexity of the combination product and the nature of the safety considerations. The human factors study evaluates: (i) the ability of the user to perform critical tasks, and (ii) the ability of the user to understand the information in the packaging and labeling, such as product labels or instructions for use, that inform the user's actions and that are critical to the safe and effective use of the combination product[1]. Minimizing use errors to the lowest possible level is essential for safe and effective nonprescription product use.

Simulated consumer interaction in the human factors studies conducted by Armstrong identified situations when there were user errors and task failures/failure modes in following the nonprescription product labeled instructions that were evaluated in human factor study G3 during the June 28, 2016 (Class 2 resubmission) review cycle. These critical task user errors were considered clinically significant performance issues and the overall risk-benefit assessment did not support approval of epinephrine HFA for the temporary relief of mild

[1] The draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016) is available on the FDA guidance web page at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm484345.pdf

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symptoms of intermittent asthma for nonprescription use. Additional information was needed to determine whether the consumers can use the epinephrine HFA product correctly using the labeled information without the intervention of a health care professional/learned intermediary. Specifically, the data reviewed in the human factors study G3 showed clinically important use errors in at least one of the three primary critical tasks (see section 3.1) and there remained clinical concerns when these critical use tasks were not correctly performed because asthmatics may not receive therapeutic dosing.

In support of the marketing application during the second resubmission on May 7, 2018 to NDA 205920, Armstrong submitted data from human factors validation study G4 using the current iteration of the product label to understand device use. Information was reviewed to determine the adequacy of the human factors study G4 and whether the user interface was improved to support nonprescription use of epinephrine HFA for the temporary relief of mild symptoms of intermittent asthma. Additional supportive CMC bench study data was submitted that supported revisions of the directions for use and making the collective tasks less cumbersome.

Based on the available information reviewed in NDA 205920, Armstrong's application adequately demonstrated that consumers can use the drug-device product safely and properly without the intervention of a health care professional using the labeled information for nonprescription use to achieve the intended effect, i.e., for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. Information reviewed in the previous review cycles for the device and dose indicator showed reliable performance over the lifespan of the product.

1.3. Benefit-Risk Assessment

Please see Jenny Kelty, MD cross discipline team lead review for NDA 205920 benefit-risk integrated assessment summary.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section where discussed, if applicable
	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	!	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		!	Patient reported outcome (PRO)	
		!	Observer reported outcome (ObsRO)	
		!	Clinician reported outcome (ClinRO)	
		!	Performance outcome (PerfO)	
		Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	!	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	!	Observational survey studies designed to capture patient experience data		
	!	Natural history studies		
	!	Patient preference studies (e.g., submitted studies or scientific publications)		
	!	Other: (Please specify)		
!	Patient experience data that were not submitted in the application, but were considered in this review:			
		!	Input informed from participation in meetings with patient stakeholders	
		!	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		!	Observational survey studies designed to capture patient experience data	
		!	Other: (Please specify)	
!	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

Please see Ryan Raffaelli, MD medical officer's clinical review of April 15, 2014 (DARRTS Reference ID: 3489745) for discussion of asthma including the discussion on the diagnostic category of interest, mild intermittent asthma; and for information on products like epinephrine available for managing acute asthma symptoms and other marketed short acting beta agonists.

To discuss briefly, patients diagnosed by their healthcare provider with mild, intermittent asthma, which is generally defined as experiencing symptoms on two or fewer days per week, use of a short-acting beta agonist for symptom control on two or fewer days per week, nighttime awakenings two or fewer times per month, have no interference of normal activities by asthma symptoms, have normal baseline lung function, and experience one or fewer exacerbations per year, are targeted for nonprescription epinephrine HFA metered dose inhaler use. The proposed indication statement in the drug facts label (DFL) for the epinephrine HFA product for nonprescription use is "for temporary relief of mild symptoms of intermittent asthma." Because patients with mild disease can experience severe exacerbations with life-threatening consequences, the epinephrine HFA metered dose inhaler product needs to be reliable given the proposed use as a rescue inhaler in the asthmatic population. Patients with more frequent or persistent symptoms should be under a physician's care and the proposed DFL includes consumer warnings to "see a doctor".

As noted above in section 1.1, epinephrine CFC metered dose inhaler was available until 2011 and marketed for nonprescription use as Primatene Mist for almost 50 years without significant safety findings. The epinephrine HFA development program focused on elements that differed from the epinephrine CFC product label.

Most importantly, because of the differences in the propellant characteristics, the epinephrine HFA suspension formulation settles easily, and therefore the inhaler must be shaken vigorously and reprimed before each use to provide consistent therapeutic dosing. If the epinephrine HFA metered dose inhaler is not shaken, this could potentially result in dose variability leading to higher doses administered. The epinephrine HFA propellant requires cleaning due to the stickiness of HFAs to prevent product occlusion. Table 1 summarizes product characteristic differences between the epinephrine CFC metered dose inhaler Primatene Mist[2] compared to the currently proposed epinephrine HFA product.

[2] See archived drug label DailyMed and summary information in Armstrong submission dated June 28, 2016 (https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=13423)

Table 1: Comparison of Epinephrine Chlorofluorocarbon MDI and Epinephrine Hydrofluoroalkane MDI

	epinephrine chlorofluorocarbon (CFC) MDI (previously marketed CFC product known as Primatene Mist)	**epinephrine hydrofluoroalkane (HFA) MDI** (proposed)
Propellant	CFC -withdrawn December 2011	HFA
Drug container	Glass reservoir	Aluminum canister
Dose indicator	Semi-transparent reservoir allowing patients to visually determine when the drug solution was running out	Attached dose counter
Formulation	Solution	Suspension
Use and care instructions	(b) (4) mouthpiece after each use	(b) (4)
Population	Ages 4 years and above	Proposed 12 years and above
Dosing regimen	1-2 inhalations every 3 hours; (b) (4)	1-2 inhalations every 4 hours; maximum 8 inhalations per day
	DRUG FACTS LABEL	
Strength	0.22 mg per inhalation	0.125 mg per inhalation
Uses	For temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath	For temporary relief of mild symptoms of intermittent asthma: wheezing, tightness of chest, shortness of breath
Warnings	**Asthma alert** Because asthma can be life threatening, see a doctor if you: • are not better in 20 minutes • get worse • need 12 inhalations in any day	**Asthma alert** Because asthma may be life threatening, see a doctor if you: • are not better in 20 minutes • get worse • need more than 8 inhalations in 24 hours

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	• use more than 9 inhalations a day for more than 3 days a week • have more than 2 asthma attacks in a week	• have more than 2 asthma attacks in a week These may be signs that your asthma is getting worse
Directions	Do not exceed dosage Supervise children using this product Adults and children 4 years and over: • start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours. Children under 4 years of age: ask a doctor	For adults and children 12 years of age and over children under 12 years of age: do not use; it is not known if the drug works or is safe in children under 12. **Before First Use**, activate new inhaler by shaking then spraying into air 4 separate times. **Each time you dose**, Shake then spray into the air one time (b) (4) Wait 1 minute. If symptoms not relieved, take a second inhalation by repeating (b) (4) **After use** Wait at least 4 hours between doses Do not use more than 8 inhalations in 24 hours Wash inhaler after each day of use. Run water through mouthpiece for 30 seconds
MDI-metered dose inhaler		

Considering the differences between the CFC and HFA epinephrine products, and that consumers who previously used the epinephrine CFC product may be familiar with and likely use the epinephrine HFA product, diligent adherence to the recommended epinephrine HFA labeled instructions is required for safe and effective use.

Each epinephrine HFA metered dose inhaler contains 160 metered sprays releasing 125 mcg of epinephrine per actuation. The proposed dose is one or two inhalations with instructions to wait at least four hours between doses, with a maximum of eight inhalations per 24 hour period. The product is a standard press-and-breathe metered dose inhaler that comes assembled.

The epinephrine HFA metered dose inhaler includes a top mounted dose actuation indicator. This device attaches to the end of the drug product canister using an adhesive label. The dose indicator mechanically counts each actuation. The display advances every 10 actuations and is

labeled numerically in increments of 20. When 20 or fewer actuations remain, the display begins to turn red in color. The red zone continues to fill the display until the counter indexes to zero. At this point the display is at the zero count and completely red, indicating the need to replace the inhaler. After the zero count has been reached, additional actuations of the metered dose inhaler no longer advance the display.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Please refer to prior NDA 205920 reviews of Theresa M. Michele, MD (May 22, 2014; DARRTS Reference ID: 3511415) and Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745) for the relevant regulatory history for epinephrine HFA metered dose inhaler. Information abstracted from the above-mentioned reviews with updated interim submission related regulatory activities is included in section 3.2 of this review.

When the metered dose inhalers using ozone-depleting CFC propellants were phased out beginning in 1996 in compliance with the Montreal Protocol, the previously marketed epinephrine CFC metered dose inhaler was withdrawn from distribution in 2011. Armstrong began communications with FDA for reformulating epinephrine without CFCs during pre-IND meeting in 2007 (IND 74,286).

An initial submission to NDA 205496 for the epinephrine HFA based inhalation aerosol was received on April 8, 2013. This first submission to NDA 205496 was refused to filed because of inadequate electronic document formatting permitting substantive review as per 21 CFR 314.101(d).

Armstrong submitted information to NDA 205920 for their reformulated epinephrine HFA metered dose inhaler product with the new propellant (instead of CFC) on July 20, 2013. NDA 205920 received a complete response letter on May 22, 2014 during that first cycle review. In the first cycle, Armstrong conducted four consumer studies, including three label comprehension studies and one behavioral human factors study evaluating whether subjects could correctly use the device using the labeled information.

FDA took a complete response action on May 22, 2014 due to product quality, nonclinical, and clinical deficiencies, with the following deficiencies outlined:

- cGMP deficiencies for the active pharmaceutical ingredient
- lack of nonclinical data supporting safety of excipient thymol for chronic use via oral inhalation

- lack of assurance that consumers can adequately use the product correctly without the intervention of a health care professional

NDA 205920 was also the subject of a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on February 25, 2014 as the epinephrine HFA product represented the only metered dose inhaler product available for nonprescription use.

Armstrong resubmitted the application for review on June 28, 2016 (Class 2 resubmission). Following review, DNDP communicated that although Armstrong made significant improvements to the user interface, Armstrong still needed to demonstrate that consumers could use the epinephrine HFA metered dose inhaler drug-device product for the intended use in the nonprescription setting (as labeled) without the intervention of a health care professional/learned intermediary for temporary relief of symptoms of mild, intermittent asthma. FDA took a complete response action on December 23, 2016.

Specifically, data reviewed in the human factors study G3 showed clinically important use errors with at least one of the three primary tasks (critical use tasks).

- (Task 1) initial priming (4shake+4spray) of the inhaler
- (Task 2) cleaning/washing of the inhaler
- (Task 3) routine use re-priming of the inhaler (1shake+1spray, and inhale)

DNDP analysis for the three primary tasks identified up to 13% of participants with errors in each of these tasks that could lead to clinically important subpotent or superpotent dosing. Because some participants had clinically important errors in more than one task, this yielded 30% of participants with an error for at least one task. It was of clinical concern if these tasks were not correctly performed because users of the epinephrine HFA nonprescription product for temporary relief of asthma symptoms would not reliably receive the correct dose. In the case of subpotent dosing, which will likely result in lack of efficacy with inadequate relief of asthma symptoms, may also result in worsening of asthma symptoms.

To resolve this second cycle review deficiency (second complete response letter issued December 23, 2016), Armstrong was recommended to conduct a human factors validation study, after re-evaluating the primary task failures and their associated root causes. DNDP recommended assessing consumer understanding and ability to complete the three primary use tasks (critical tasks) with the epinephrine HFA inhalation aerosol for: (1) initial priming of the inhaler, (2) cleaning/washing of the inhaler to prevent clogging, and (3) routine use (repriming) of the inhaler. Armstrong needed to further optimize labeling with information from the supportive human factors study demonstrating that consumers can appropriately use the device with the revised labeling. In addition to the DNDP recommended changes that were already adopted in the DFL, the consumer instructions for use, and the outer carton, further

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changes were recommended for the device labeling regarding the mouthpiece instructions to make the instructions for use present on the orange-colored actuator both visible and consistent with the consumer instructions for use by adding pictograms for the key steps for safe and effective use.

Armstrong filed a formal dispute resolution request (FDRR) on June 27, 2017 to appeal the second complete response letter deficiencies (December 23, 2016), and requested that the data from the previously conducted human factors study G3 be considered adequate to support approval of epinephrine HFA. Additional CMC bench studies data were submitted during the FDRR. Armstrong's FDRR appeal was denied on September 1, 2017 and in the denial letter FDA indicated that additional CMC information (from studies that evaluated user errors) will be reviewed during the next NDA resubmission.

See section 8.1 for review of the response to FDA's December 23, 2016 complete response action letter.

3.2. Summary of Presubmission/Submission Regulatory Activity

Information included in this section is abstracted from NDA 205920 reviews of Theresa M. Michele, MD (May 22, 2014; and December 23, 2016 DARRTS Reference ID: 4033296) and Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745) with updated interim submission related regulatory activities.

IND 74286

March 27, 2007 pre-IND meeting

- Discussion of proposed epinephrine HFA MDI development program, including requirements for clinical efficacy and safety, consumer behavior studies, and data to support the reliability and robustness of the device and dose counter.

November 25, 2008 Communication

- Feedback provided on clinical trial design

October 26, 2009 IND submitted

- Feedback provided on proposed development program, including the need for detailed monitoring of cardiovascular vital signs, pharmacokinetic sampling, long-term safety data, consumer studies, and data to support the chemistry, manufacturing, and controls of the product.

October 29, 2010 EOP2 Meeting

- Dose-ranging did not appear to be adequate; exposure of 125 mcg dose higher than reference product; recommendation to explore doses lower than 125 mcg
- Recommendation for larger and longer pediatric clinical trial
- Include reference product in phase 3 trials

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- Assess device performance, including ruggedness and reliability

May 10, 2011 Communication

- Based on preliminary results of the dose ranging trials, FDA recommended carrying forward the epinephrine HFA 125 mcg dose into the phase 3 program, noting that the systemic exposure from 125 mcg is higher than that with epinephrine CFC 220 mcg, a difference that will have to be supported by phase 3 data and addressed in the NDA

September 23, 2011 preNDA meeting

- Reiteration of the need for a minimum of 6 months of safety data
- A large (n~300) label comprehension/behavioral use trial is required
- Concerns raised regarding the product's potential need for once-daily cleaning
- FDA requested device performance data under different in-use conditions to assess the impact of not cleaning the mouthpiece as directed
- Reminder to assess potential malfunctioning of the device with real-life usage
- Recommendation that the Sponsor request a second pre-NDA meeting upon the completion of phase 3

January 26, 2012 Communication

- Feedback provided on proposed long-term safety trial
- Requested safety data from at least 300 patients exposed for 6 months, which could be generated from already ongoing trials or from a new separate long term safety trial
- Requested pharmacodynamic data (i.e., blood pressure, heart rate)
- Deferred discussions of the pediatric program until efficacy and safety data in adults and adolescents were available

April 23, 2012 Communication

- Feedback provided on proposed label comprehension study

January 31, 2013 2nd preNDA meeting

- Recommendations on submission of specific pharmacodynamic data, AEs, serial FEV1 data and literature review in NDA submission
- Recommendation that NDA submission include evaluations of device performance during real-life use, evidence of device ruggedness, and a discussion of the potential for device clogging as well as justification for device cleaning instructions
- Concerns raised regarding adequacy of data in pediatric patients 4 to 11 years of age. Armstrong stated they may submit the NDA for adults 18 years of age and older. FDA raised concern that the epinephrine CFC Primatene Mist product was labeled down to 4 years of age and consumers may use an epinephrine HFA product in patients down to 4 years of age. FDA advised the sponsor to submit all pediatric data with the NDA application, even if the age range proposed for approval is limited to adults.

<u>NDA 205496</u>

April 8, 2013 NDA 205496 submitted for epinephrine HFA (refuse to file)

- The application had several deficiencies that precluded substantive review (refuse to file

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letter issued July 7, 2013)

NDA 205920

July 22, 2013 (initial NDA review)

- NDA 205920 resubmitted for epinephrine HFA and accepted for filing
- A new NDA number (NDA 205920) was provided because of the vast technical problems associated with the original NDA (205496) submission.

October 1, 2014 End of Review Type A meeting

- Discussion of proposed qualification program for the excipient thymol
- Recommendation to submit the results of the label comprehension and human factors studies for review and request a meeting to discuss study findings and the need for an actual use trial

May 22, 2014 Complete Response action

- product quality, nonclinical, and clinical deficiencies identified:
- cGMP deficiencies for the active pharmaceutical ingredient
- lack of nonclinical data supporting safety of excipient thymol for chronic use via oral inhalation
- lack of assurance that consumers can adequately use the product correctly without the intervention of a health care professional

January 22, 2016 FDA advice letter

- Feedback for protocol design for the human factors trial appeared adequate
- Recommendations regarding sampling times, negative control group, and toxicokinetic measurements for the nonclinical study

June 28, 2016 Class 2 resubmission (second cycle NDA review)

- Human factors study (G3)
- User interface improvements
- CMC bench study data

December 23, 2016 Complete Response action

- Human factors study G3 failed to demonstrate that the user interface supports safe and effective use of the product by intended users for the proposed uses in the nonprescription setting.
- Human factors study G3 had approximately 30% of participants who failed at least one of the three primary tasks (critical use tasks) of the study: initial priming of the inhaler (Task 1), cleaning of the inhaler (Task 2), or routine use (re-priming) of the inhaler (Task 3). Because some participants had clinically important errors in more than one task, this yielded 30% of participants with an error for at least one task

September 2, 2017 Formal Dispute Resolution Request

- Appeal denied

March 2, 2018 FDA advice letter

- Feedback provided for human factors study G4 protocol design

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May 7, 2018 Class 2 resubmission (third cycle NDA review)

- complete response to deficiencies identified during the second cycle in the letter dated December 23, 2016, the formal dispute resolution request appeal denied letter dated September 2, 2017, and the general advice letter dated March 2, 2017

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

To resolve deficiencies outlined in the second complete response letter issued December 23, 2016, Armstrong was recommended to conduct a human factors validation study, after re-evaluating the three primary use tasks (critical tasks) and their associated root causes, including an assessment of consumer understanding and ability to complete the primary use tasks with the epinephrine HFA inhalation aerosol.

Grace P. Jones, PharmD, BCPS, Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors validation study report G4 and Muthukumar Ramaswamy, PhD, reviewed additional CMC bench data for the drug product provided to support directions for use and product labeling. Additional information supporting NDA 205920 and any applicable review discipline summaries may be obtained from prior NDA 205920 clinical reviews of Francis E Becker, MD (December 09, 2016; DARRTS Reference ID: 4025825) and Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745).

5. Sources of Clinical Data and Review Strategy

There was no clinical trial data submitted to resolve deficiencies outlined in the second complete response letter issued December 23, 2016.

Please refer to prior NDA 205920 clinical reviews of Theresa M. Michele, MD (May 22, 2014; DARRTS Reference ID: 3511415), Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745), and Francis E Becker, MD (December 09, 2016; DARRTS Reference ID: 4025825) for discussions of the clinical efficacy and safety data supporting marketing application for epinephrine HFA metered dose inhaler. Armstrong submitted materials for review of their complete response letter to the December 23, 2016 letter via eCTD submission \\CDSESUB1\evsprod\NDA205920\0071

Information regarding the product, and any relevant safety and efficacy information from the

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above-mentioned reviews are abstracted and included where applicable for discussion, and to provide additional clinical context to the DMEPA and Drug Product quality assessment reviewers' recommendations to support directions for use and product labeling.

6. Review of Relevant Individual Trials Used to Support Efficacy

There was no clinical trial data submitted in the May 7, 2018 NDA class 2 resubmission.

7. Integrated Review of Effectiveness

See section 1.2.

8. Review of Safety

8.1. Integrated Assessment of Safety

There was no new clinical trial data submitted for the assessment of safety in the May 7, 2018 NDA class 2 resubmission.

Previously reviewed safety data for epinephrine HFA from the adult phase 3 clinical trial data that included a review of the cardiac safety of epinephrine HFA in addition to postmarketing reports of adverse events with epinephrine CFC did not identify serious safety signals, and the reviewed safety data was considered acceptable for approval. Considering the known pharmacologic and physiologic effects of epinephrine, and the higher systemic exposure for the proposed epinephrine HFA product dose of 125 mcg per actuation (4.5 times increase in C_{max}) when compared to the previously marketed epinephrine CFC Primatene Mist product dose of 220 mcg per actuation, several pharmacodynamic safety measures indicated that resultant drug levels at doses nearly 13-fold higher with epinephrine HFA product (125 mcg per actuation versus 1600 mcg in a high dose PK study in healthy volunteers) were not likely associated with significant safety issues. The high dose PK study in healthy volunteers demonstrated substantial increases in blood pressure (>50 mmHg systolic) and pulse (>60 bpm) in some patients 10 minutes after a single dose of 1250 mcg and 1600 mcg, although the median increases were more modest (pulse increase of 5-6 beats, systolic blood pressure increase of 9-14 mmHg, diastolic blood pressure increase of 1-3 mmHg). To achieve a dose of 1250 mcg, ten

Reference ID: 4338147

inhalations of the proposed 125 mcg dose in rapid succession should be administered; a dose of 1600 mcg would require 12-13 inhalations. Importantly, there was no data identifying a cardiovascular safety concern when the product was used at the proposed labeled maximal dose of 250 mcg (After 1 inhalation, wait 1 minute. If symptoms not relieved, take a second inhalation by repeating shake then spray into the air once before inhalation), giving some idea of the safety margin available in the case of overdose importantly when the product may be used at higher doses than recommended, or if a superpotent dose should be delivered with an actuation.

Human Factors (Behavioral) Study

Sections 1.1 and 2 discussed the information needed to support epinephrine HFA marketing focusing on elements that differed from the previously available epinephrine CFC Primatene Mist product label. Information was needed from the human factors behavioral study based on the consumer understating of labeled packaging instructions, including the DFL, and the consumer instructions for use to determine safe and effective use of the product with the objective of minimizing use errors to the lowest possible level when the epinephrine HFA product was used in the nonprescription setting without the oversight of a learned intermediary.

Response to FDA’s December 23, 2016 Complete Response Action Letter

DNDP provided several labeling recommendations during the second cycle NDA review prior to the complete response letter issuance that were already adopted by Armstrong in the DFL, the consumer instructions for use, and the outer carton.

Armstrong drastically modified the consumer instructions for use from what was used in the human factors study G3, with simplified steps so that information was now presented only on one side of the page, and aligning the instructional language on the actuator to the revised DFL and consumer instructions for use. Carton box modifications were made requiring the consumer instructions for use information insert to be removed prior to using the inhaler. Information from the CMC bench studies, conducted prior to human factors study G4, supported the revised information in the instructions for use tested in human factors study G4. Armstrong additionally modified the labeling on the device actuator and mouthpiece with pictograms incorporating DNDP recommendations considering that the user may not have immediate access to the DFL or consumer instructions for use when the inhaler is being used. Re-testing these changes in a human factors study was considered necessary because there were no prescription inhaler products with a similar presentation. DNDP considered it a reasonable approach to proceed with human factors testing given that the major elements being tested were related to instructions for use. Because the DFL and consumer instructions for use were changed substantially after the previous label comprehension studies, the human factors study was much more relevant to the overall expected use of the product by consumers.

Please refer to Grace P. Jones, PharmD, BCPS, Division of Medication Error Prevention and Analysis (DMEPA) review and recommendations of the human factors validation study report G4. DMEPA noted that the human factors validation study G4 results demonstrated that the intended user population can use the proposed epinephrine HFA product safely and effectively. DMEPA provided editorial recommendations for maintaining consistency with the information across the various labeling pieces.

Reviewer comments

Assessment of the three primary critical tasks tested in the human factors validation study G4 were found acceptable during DMEPA review, to inform labeling:
Task 1: initial prime –shake then spray into the air 4 times.
Task 2: routine use (dosing) –shake the inhaler before taking a dose
Task 3: washing procedure –rinse water through both ends of the mouthpiece for at least 30 seconds

Initial prime –shake then spray into the air 4 times

Anticipating clinical situations during product use, as was shown in the human factors study G4, some participants did not adhere to the labeled instructions to shake then spray into the air four times for initial prime or activation of the epinephrine HFA metered dose inhaler. While all participants in human factors study G4 met the minimal acceptance criteria to at least shake then spray one time (epinephrine HFA proposed labeling states shake then spray into the air four times), performance of the (minimal) shake then spray one time procedure was shown in the CMC bench data to result in a partial or suboptimal or subpotent delivery of first dose administered (i.e., for the emitted second spray). Failure to deliver a dose of a rescue inhaler during an acute asthma attack could result in serious outcomes if the consumer is unable to seek immediate medical assistance. However, the labeled directions permit a repeat or additional dose after one minute for asthma relief, and this label permitted second dose will provide the therapeutic dose as per the reviewed CMC bench data (i.e., for the emitted third spray). Concern of administering a superpotent dose or overdose in the absence of performance of labeled task 1 or routine use task 2 may result in an increased incidence of adverse effects, although the products safety profile discussed above did not identify serious safety signals based on the higher systemic exposures observed.

Inhaler repriming frequency for routine use

Shaking (Task 2) is critical for adequate therapeutic dose administered during intermittent episodes of asthma for the temporary relief of mild symptoms experienced because of the suspension nature of the epinephrine hydrofluoroalkane metered dose inhaler product.

Armstrong's August 2017 submission stated that in the inverted position (the position that the inhaler is held during use), the Active Pharmaceutical Ingredient (API) (b) (6)

Figure 1: Inverted Orientation of Epinephrine HFA MDI at Storage and at Use

Position	Orientation at Storage (not Spray)		Orientation at Use (at Spray)	
	Inhaler Unit	Canister Unit	Inhaler Unit	Canister Unit
Inverted				(b) (4)

Source: eCTD submission \\CDSESUB1\evsprod\NDA205920\0065, (August 17, 2017). Module 1.11.4. Supplemental Device Study Report for Under and Supra-Therapeutic Dosing Risk Evaluation due to User Error of "No Shaking". Table 1: Three (3) Positions of Storage.

Shaking minimizes the risk for variability in the dose provided and variability in the dose content uniformity such that settled suspension becomes uniform and provides the most optimal dose for the user. Not shaking the inhaler before first use (initial priming stage) or during routine use (repriming or prior to taking the dose) will result in either subpotent dose or superpotent dose.

The label reviewed during the June 28, 2016 (Class 2 resubmission) review cycle included evaluation of the task to spray after shaking prior to dosing (repriming), and this information in labeling was considered acceptable. After issuance of the December 23, 2016 complete response, Armstrong made considerable improvements to the consumer instructions for use and the actuator label including simplified labeling instructions. Human factors study G4, task 2, evaluated if the newly proposed user interface, (b) (4)

Dr. Ramaswamy noted that the epinephrine HFA inhaler (b) (6) the emitted dose content of the first dose from the inhaler may be lower than the expected after a period of non-use (after the task 1 initial prime –shake then spray into the air 4 times), resulting in underdosing or delivering a subpotent dose. Armstrong obtained repriming frequency data from more than one study simulating use conditions (b) (4)

(b) (4) I concur with Dr. Ramaswamy's conservative labeling recommendation to reprime before each time the epinephrine HFA is used to administer a dose, to provide consistent therapeutic dosing.

After the initial priming activation step when the product is initially obtained, considering the information from the various supportive CMC bench data reviewed, DNDP is recommending the most conservative labeling directions for each subsequent dosing. More importantly *repriming* or reactivating the device with shaking *and spraying* in the air prior to each inhalation (b) (4) is considered for optimal use.

Inhaler Washing/Cleaning frequency

(b) (4) CMC bench study data obtained since the December 23, 2016 complete response action, which indicated that the use of dirty inhalers beyond seven days of use without cleaning will result in the delivery of inconsistent dose.

The new CMC bench study data reviewed did not report actuator clogging indicating that the risk of subpotent dosing is low over the container life, as the delivered dose content did not gradually decrease over the twenty days simulated use period without cleaning. When the average dose content of the first two sprays dispensed was taken together, utilizing supporting labeled information that permitted administration of a second dose after a minute of inadequate relief of the asthma symptoms, the two spray CMC bench study data did not show evidence of subpotent doses delivered, and therefore was reassuring. However, without washing the actuator beyond seven days may result in situations when the asthmatic will likely receive superpotent dosing, especially with the first of two recommended inhalations per the labeled instructions for use. There is medication build-up or accumulation resulting in higher than expected dose content due to dose carry over from the actuator.

Dr. Ramaswamy's September 27, 2018 CMC review additionally included information comparing the orifice diameter of the proposed epinephrine HFA actuator (b) (4) mm) to other albuterol sulfate aerosol inhalers ((b) (4) mm) that discussed drug load per actuation and alcohol content of the proposed epinephrine HFA actuator during simulated use for the inhaler life of 160 sprays over 20 days explaining that the proposed epinephrine HFA product did not appear to clog in comparison to other commercially available inhalers. Based on Armstrong's experimental data shown in Table 2, it appears the orifice diameter for the proposed epinephrine HFA product is (b) (4) than that for the albuterol HFA metered dose inhaler products.

Table 2: Comparison of Epinephrine HFA MDI and Albuterol HFA MDI

Product	**Proventil HFA**	**ProAir HFA**	**Epinephrine HFA**
Formulation			
API name	Albuterol Sulfate	Albuterol Sulfate	Epinephrine
Amount of alcohol, %	(b) (4)		1.0%
Delivery amount per spray			
Total amount per actuation, mg	(b) (4)		
Actuator orifice			
Diameter of orifice, mm			
Section area of the orifice			
Ratio of orifice section area, vs. ProAir			

Source: eCTD submission \\CDSESUB1\evsprod\NDA205920\0065, (August 17, 2017). Module 1.11.4. Supplemental Device Study Report for Under-Dosing Risk Evaluation, Table 4.
*from experimental data

During several rounds of review discussions and labeling meetings, the review team agreed that the consumer's benefitted from washing the inhaler more frequently (b) (4) to provide consistent dosing and for maintaining a clean device for subsequent uses. Dr. Ramaswamy's CMC product quality review discussed that while the original (previously conducted) cleaning study data supported three days of use without inhaler cleaning and the recently reviewed data suggested seven-day interval wash frequency, the originally proposed labeling instruction in the June 28, 2016 (Class 2 resubmission) "Wash every day if used" was very conservative. Recommendation to instruct consumers to wash the inhaler after "each day of use" was found acceptable by the review team instead of the proposed (b) (4) (b) (4) the more conservative and direct reminder to wash after each day of actual use was optimal for safe and effective use.

Number of Actual Doses Available per Epinephrine HFA Nonprescription Labeling

During internal meetings for NDA 205920 class 2 resubmission the review team discussed the proposed number of actuations per inhaler (160 sprays) considering the concerns raised during the joint meeting of the Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committees (February 25, 2014) that the availability of a high number of actuations per inhaler could encourage continued use for prolonged durations that may result in delayed health care provider visits. The availability of the epinephrine HFA product for nonprescription use should not be viewed by the consumer as an alternative to being under the care of a healthcare provider for managing their asthma. Please refer to prior NDA 205920 clinical review of Ryan

Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745) section 9.3 for the summary of these deliberations by the advisory committee.

DNDP's determination for approvability of epinephrine HFA for nonprescription use took into consideration the number of doses for marketing based on the national guidelines for asthma management developed by the National Institutes of Health (NIH)[3], product labeling, the Advisory Committees' deliberations and data submitted in the NDA.

For any packaging recommendations to mitigate or limit the available inhalations per epinephrine HFA metered dose inhaler, DNDP considered the information for the labeled steps which included the initial metered dose inhaler activation (wasting 4 priming sprays), and accounting for the subsequent repriming steps (80 repriming sprays) prior to each dosing. Of the 160 total sprays, the proposed inhaler presentation is expected to provide 80 usable inhalations suitable for 10 days of labeled nonprescription use, i.e., 10 x 8 sprays per day based on labeled recommendation for no more than 8 inhalations in 24 hours.

The NIH guidelines for the diagnosis and management of asthma classify asthma severity as intermittent when symptoms occur on two or fewer days per week, which is the targeted population for the nonprescription epinephrine HFA metered dose inhaler use, for "the temporary relief of mild symptoms of intermittent asthma." When used as recommended up to the maximum recommended eight inhalations during a 24 hour period, and while adhering to warnings to see a doctor when experiencing more than two asthma attacks in a week, the epinephrine HFA metered dose inhaler user may use up to 16 inhalations in a week. Therefore, during a month, for the symptomatic control of intermittent asthma symptoms based on the conservative labeling recommendations per the DFL and consumer instructions for use, 64 usable inhalations are suitable for eight days of labeled nonprescription use. As discussed above, the proposed inhaler presentation is expected to provide 80 usable inhalations suitable for 10 days of labeled nonprescription use, i.e., 2 more days of use.

The expected users of the epinephrine HFA metered dose inhaler are asthma patients diagnosed with mild asthma who are managed with short acting beta agonists and or other asthma control prescription medications, and are occasionally in need of an acute asthma relief medication that can be obtained as a nonprescription product between the next prescription refill or interval healthcare visits. There may also be the situations when the user's regular prescription acute asthma relief medication may not be available because of travel or the prescription medications are not easily accessible to them during the acute episode for symptom control because of their very intermittent symptoms experienced. In these circumstances the nonprescription epinephrine HFA metered dose inhaler is expected to

[3] Busse, W, Panel Chair, 2007, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (http://www.nhlbi.nih.gov/guidelines/asthma/index.htm; accessed October 8, 2018)

Reference ID: 4338147

provide relief. It is conceivable that asthma patients in some geographic locations of the United States may not have access to a healthcare provider regularly for adequate asthma management. In these circumstances, it is most helpful to have the nonprescription epinephrine HFA product available for managing their intermittent asthma symptoms until their next visit with a healthcare provider for poor symptomatic control (b) (4) The proposed inhaler presentation with 160 total sprays expected to provide 80 usable inhalations suitable for 10 days of labeled nonprescription use appears acceptable for clinical use and does not pose any additional risk.

However, to mitigate situations whereby prospective nonprescription users of the proposed epinephrine HFA product who have been diagnosed previously with asthma (as per the epinephrine HFA label) and choose to not have their asthma care further managed by a healthcare provider because of the availability of epinephrine HFA for nonprescription use, alternate packaging configurations are to be considered. The reviewer recommends measures to mitigate the risk of deferred care for poorly controlled asthma with package limitations or preventing co-packaging of the epinephrine HFA inhalers in multipacks for nonprescription use. Communications with Armstrong and to future generic product sponsors is additionally recommended to deter manufacturing larger than the 160 spray fill sizes of the drug packaged in the metered dose inhaler.

9. Advisory Committee Meeting and Other External Consultations

A joint meeting of the Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committees was held on February 25, 2014 to discuss the efficacy, safety and overall benefit-risk profile of the product for the treatment of mild symptoms of intermittent asthma in the nonprescription use setting. Please refer to Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745) NDA 205920 clinical review for the advisory committees' deliberations and for summary discussions and comments for considering the proposed epinephrine HFA metered dose inhaler for approval. 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 September 26, 2018).

10. Labeling Recommendations

10.1. Nonprescription Drug Labeling

The proposed DFL for epinephrine HFA provides indication for "the temporary relief of mild symptoms of intermittent asthma" which includes patients with intermittent asthma only. In addition, the label contains a "Do not use unless a doctor said you have asthma." This indication and warning are consistent with the previously marketed epinephrine CFC product. Labeling discussions and recommendations have been discussed in several sections of the review. Please see separate DNDP labeling reviews, that include review and recommendations for the proposed website and the instructional videos.

11. Risk Evaluation and Mitigation Strategies (REMS)

Routine postmarketing surveillance is appropriate.

12. Postmarketing Requirements and Commitments

Please refer to prior NDA 205920 clinical review of Ryan Raffaelli, MD (December 19, 2016; DARRTS Reference ID: 4026312) section 1.4 for the recommendations requiring pediatric studies under the Pediatric Research Equity Act (PREA).

DNDP discussed NDA 205920 with the FDA's internal pediatric review committee (PeRC) on November 16, 2016. PeRC agreed that a partial waiver was acceptable because children under four years do not have the dexterity or coordination of efforts to reliably manipulate the inhaler device, therefore clinical studies in this age group would be impossible or highly impracticable.

Required PREA studies included the conduct of deferred multiple dose safety and efficacy trial with three arms in 4 to 11 years 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} (b) (4) in the safety and efficacy trial. PeRC did not consider it necessary to conduct a separate PK study, as discussed in Jianmeng Chen, MD PhD December 9, 2016 clinical pharmacology review.

13. Appendices

13.1. References

See footnote references and in-text references.

13.2. Financial Disclosure

Not applicable.

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/

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10/22/2018

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