

CLINICAL REVIEW

Application Type NDA
Application Number(s) 205920
Priority or Standard Standard

Submit Date(s) June 28, 2016
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Division / Office DNDP/ODE IV

Reviewer Name(s) Ryan Raffaelli
Review Completion Date December 12, 2016

Established Name Epinephrine Inhalation Aerosol
(Proposed) Trade Name Primatene Mist
Therapeutic Class Nonselective adrenergic
receptor agonist/ bronchodilator
Applicant Armstrong Pharmaceuticals,
Inc.

Formulation(s) Aerosol, metered (125 mcg/
inhalation)
Dosing Regimen 1-2 inhalations every 4 hours
as needed; maximum 8
inhalations/24 hours
Indication(s) Temporary relief of mild
symptoms of intermittent
asthma

Intended Population(s) 12 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

No clinical data were submitted in this application, thus, this reviewer relinquishes recommendation on regulatory action to a synthesis of the other discipline reviews.

The following were deficiencies outlined in the Complete Response Letter of May 22, 2014:

- 1) FDA required resolution of post-inspection current good manufacturing practice (cGMP) deficiencies at the [REDACTED] facility (b) (4)
- 2) Data supporting safety of chronic inhalation of thymol is required
- 3) Labeling requires significant revision and testing in label comprehension study to ensure understanding of certain critical information: priming before first use, daily cleaning when used, repriming when the inhaler is wet, not to rely on the dose indicator if dropped, disassembly/reassembly for cleaning, pressing on the center of the indicator for dosing, and orientation of the inhaler during use and storage
- 4) FDA required behavioral testing (human factors) with optimized labeling to reassess ability to use and properly care for the product
- 5) FDA required a randomized actual use trial to quantify and analyze problems with use and characterize sources of error. We recommended that randomization take place with a marketed bronchodilator product comparator.

Reviewer's comments: With regard to #5, the actual use trial, FDA and the applicant discussed the need for one at a Type A meeting following the Complete Response (see Section 2.5 below for details on the pre(re)submission regulatory activities).

Since no clinical data were submitted for review, the findings from label comprehension studies (Ms. Cohen's and Dr. Zhao's reviews), the human factors study (reviews by Drs. Jones and Zhao), nonclinical study (Dr. Thompson's review) and the quality assessment (Dr. Muthukumar's review) will inform the recommendation on regulatory action.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

If approved, a partial waiver is acceptable, and an additional pediatric trial is required under the Pediatric Research Equity Act (PREA). Similar to the first review cycle, the applicant submitted a request for partial waiver of trials in children under the age of four. Trials in this age group would be impossible or highly impracticable (Section 505B(a)(4)(A)(i), Federal Food, Drug and Cosmetic Act (FD&C Act)). Children under 4 years do not have the dexterity or coordination of efforts to reliably manipulate the inhaler device. In fact, nebulized medications are cornerstones of current practice in this population. 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. The Pediatric Review Committee (PeRC) agreed with the partial waiver.

The applicant must conduct a multiple dose safety and efficacy trial with three arms in pediatric subjects with asthma 4 to 11 years of age comparing a two-inhalation dose of the test product, epinephrine inhalation aerosol (125 mcg/inhalation), a one-inhalation dose of the test product, and placebo. The trial must include an assessment of epinephrine exposure around Tmax (b) (4). See the brief review by Dr. Chen (Office of Clinical Pharmacology) with further discussion about the PK component of the trial. (b) (4)

(b) (4) Consistent with the timeline (letter of April 9, 2014) proposed by the applicant regarding submission of final study reports during the first review cycle, PeRC agreed that one year post-approval was reasonable to submit a protocol for review, conduct the trial and submit a final report. Thus, if approved, a final study report would be submitted in January 2018. However, this is negotiable with the applicant to come to agreement on a reasonable timeline.

The PeRC met on November 16, 2016 to discuss this application and agreed with the division on deferral of the required trial and the partial waiver.

2 Introduction and Regulatory Background

Since there were no clinical data submitted, this document only provides a brief update of regulatory activities since the Complete Response, comments on the proposed labeling (**Section 9.2**) and a statement about required postmarketing pediatric studies under PREA. Information in this officer's original review document will not be repeated here. Numbering for this review follows the clinical template, but missing headers are purposeful and not relevant to this review.

2.1 Product Information

See this medical officer's clinical review of April 15, 2014 (DARRTS) for details on product and presubmission regulatory activities.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Following the Complete Response, the applicant requested a meeting with FDA held on October 1, 2014. At the meeting, we discussed assessment of thymol safety and the need for data on comprehension of important labeling messages to ensure proper use of the product. The applicant committed to addressing all deficiencies listed in the Complete Response letter. With regard to #5 in **Section 1.1**, FDA deferred discussion of an actual use trial until it had an opportunity to review findings from the label comprehension and human factors assessments. FDA advised the applicant to request a meeting to determine if an actual use trial was needed. At that time, the applicant agreed. In May 2016, the applicant submitted the protocol for study G3, the human factors assessment, to the IND (74286). The next formal communication with the applicant and document submission included the application resubmission for approval.

Reviewer's comment: The applicant declined to seek advice on designing and conducting an actual use trial. This was their prerogative, but as noted above, consideration of such a trial was our advice to which the applicant initially agreed.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the quality of the electronic submission was adequate. The sections reviewed were reasonably well-organized with working hyperlinks for ease of review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

See Cross Discipline Team Lead, Dr. Frank Becker's, review and the original clinical reviews.

5 Sources of Clinical Data

No clinical data submitted.

6 Review of Efficacy

See original clinical reviews.

7 Review of Safety

See original clinical reviews.

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/s/

RYAN M RAFFAELLI
12/12/2016

FRANCIS E BECKER
12/19/2016