# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA Number:** | 021-254 (IND 57,151) |
| **Brand Name:** | Advair HFA |
| **Generic Name:** | Fluticasone propionate/Salmeterol xinafoate |
| **Sponsor:** | GlaxoSmithKline (GSK) |
| **Submission Type:** | Labeling supplement 9; PLR conversion |
| **Dosage Form:** | Metered dose inhalation aerosol |
| **Indication:** | Long-term treatment of asthma (≥12 year old) |
| **Submissions Dates:** | January 31, 2011 (SDN 207) |
| **OND Division:** | Pulmonary, Allergy, and Rheumatology Products |
| **OCP Division:** | Clinical Pharmacology II |
| **Primary Reviewer:** | Arun Agrawal, Ph.D. |
| **Secondary Reviewer:** | Suresh Doddapaneni, Ph.D. |

## TABLE OF CONTENTS

## 1. EXECUTIVE SUMMARY

Advair HFA was approved in June 2006 for long term treatment of asthma in patients ≥12 year old. Labeling supplement 9 was submitted on June 25, 2009 to provide for revised labeling in accordance with PLR format. Aproval letter dated January 4, 2011 for supplement S0012 (proposed modifications to approved REMS) requested updates to all pending supplemental applications with the content of the approved labeling. The purpose of the current amendment to supplement 9 (SDN 207) is to provide updated draft labeling that incorporates changes approved by the FDA on January 4, 2011. GSK conducted 2 pediatric PMC studies in the 4-11 year old population and submitted their reports to FDA on 01/23/2009 (SDN 160) (for details, please see Clinical Pharmacology review by Dr. Arun Agrawal). In the current amendment, GSK also included data from the 2 pediatric PMC studies. However, GSK is not seeking an asthma indication for the Advair HFA in children 4-11 years of age (please note that a dry powder inhaler of Advair containing 100 mcg fluticasone propionate and 50 mcg salmeterol xinafoate (Advair Diskus), one inhalation twice daily, was approved for use in asthmatic children 4 years of age and older on 04/21/2004).

### 1.1 Recommendation

The application is acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the agency regarding the language in the label. Labeling comments should be conveyed to the sponsor as appropriate.

### 1.2 Phase IV Commitments

None

## 2. QUESTION BASED REVIEW

Not Applicable

## 3. DETAILED LABELING RECOMMENDATAIONS

The labeling recommendations for Section 8: Use in Special Populations (Section 8.4: Pediatric Use), and Section 12: Clinical Pharmacology (Section 12.2: Pharmacodynamics, and Section 12.3: Pharmacokinetics) of the label proposed by the Agency are shown below. Deletions are shown as "~~strikethrough~~" and additions are shown as "underlined". It should be noted that entire language in section 8.4 is proposed by the Agency while GSK added language in sections 12.2 and 12.3. GSK's proposed language in sections 12.2 and 12.3 is acceptable.

### 8.4 Pediatric Use

The pharmacokinetics and pharmacodynamic effect on serum cortisol of 21 days of treatment with Advair HFA 45/21 (2 inhalations twice daily with or without a spacer) or Advair Diskus 100/50 (1 inhalation twice daily) was evaluated in a study of 31 children aged 4 to 11 years with mild asthma. Systemic exposure to fluticasone propionate was (b) (4) lower with Advair HFA (b) (4)

(b) (4) with a spacer, (b) (4) Advair Diskus. There were reductions in serum cortisol from baseline in all treatment groups (14%, 22%, and 13% for Advair HFA, Advair HFA with a spacer, and Advair Diskus, respectively) *[see Clinical Pharmacology (12.2, 12.3)]*.

**12.2 Pharmacodynamics**

Advair HFA:

*Hypothalamic-Pituitary-Adrenal Axis Effects:*

(b) (4)

**12.3 Pharmacokinetics**

Absorption:

*Fluticasone Propionate:*

*Patients With Asthma:*

The effect of 21 days of treatment with Advair HFA 45/21 (2 inhalations twice daily with or without a spacer) or Advair Diskus 100/50 (1 inhalation twice daily) was evaluated in a study of 31 children aged 4 to 11 years with mild asthma. Systemic exposure to fluticasone propionate was similar with Advair Diskus and Advair HFA with a spacer (138 pg•hr/mL [95% CI: 69, 273] and 107 pg•hr/mL [95% CI: 46, 252], respectively) and lower with Advair HFA without a spacer (24 pg•hr/mL [95% CI: 10, 60]).

*Salmeterol:*

*Patients With Asthma:*

The effect of 21 days of treatment with Advair HFA 45/21 (2 inhalations twice daily with or without a spacer) or Advair Diskus 100/50 (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol was similar for Advair HFA, Advair HFA with a spacer, and Advair Diskus (126 pg•hr/mL [95% CI: 70, 225], 103 pg•hr/mL [95% CI: 54, 200], and 110 pg•hr/mL [95% CI: 55, 219], respectively).

---

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

---

/s/

---

ARUN K AGRAWAL
07/05/2011

SURESH DODDAPANENI
07/06/2011