

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 21-254**

**PROPRIETARY NAME REVIEW(S)**

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY  
(DMETS; WO22; Mail Stop 4447)**

<b>DATE RECEIVED:</b> 2/16/06	<b>DESIRED COMPLETION DATE:</b> 5/19/06	<b>OSE CONSULT #:</b> 06-0049
<b>DATE OF DOCUMENT:</b> 12/7/05	<b>PDUFA DATE:</b> 6/8/06	

**TO:** Badrul Chowdhury, MD  
Director, Division of Pulmonary and Allergy Products  
HFD-570

**THROUGH:** Alina Mahmud, RPh, MS, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support, HFD-420

**FROM:** Felicia Duffy, RN, BSN, MSED  
Division of Medication Errors and Technical Support, HFD-420

<b>PRODUCT NAME:</b>  <b>Advair® HFA</b> (Fluticasone Propionate and Salmeterol Inhalation Aerosol) 45 mcg/21 mcg per actuation 115 mcg/21 mcg per actuation 230 mcg/21 mcg per actuation	<b>SPONSOR:</b> GlaxoSmithKline
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**NDA #:** 21-254

**SAFETY EVALUATOR:** Felicia Duffy, RN

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Advair HFA. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Advair HFA acceptable from a promotional perspective.

**Division of Medication Errors and Technical Support (DMETS)  
Office of Surveillance and Epidemiology  
HFD-420; WO22; Mail Stop 4447  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** April 17, 2006

**NDA#:** 21-254

**NAME OF DRUG:** **Advair<sup>®</sup> HFA**  
(Fluticasone Propionate and Salmeterol Inhalation Aerosol)  
45 mcg/21 mcg per actuation; 115 mcg/21 mcg per actuation;  
230 mcg/21 mcg per actuation

**NDA HOLDER:** GlaxoSmithKline

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570), for assessment of the proprietary name, "Advair HFA", regarding potential name confusion with other proprietary or established drug names. The sponsor is currently marketing Advair Diskus as an inhalation powder containing fluticasone propionate and salmeterol. Advair Diskus, which was approved on August 24, 2000, is available in the following strengths: 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg per actuation. The currently marketed Advair Diskus is propelled by patient inhalation. Advair HFA is a metered-dose aerosol that will be an addition to the Advair product line. Draft container labels, carton, and insert labeling were provided for review and comment.

**PRODUCT INFORMATION:**

Advair HFA is a combination product that contains the active ingredients fluticasone propionate as the corticosteroid and salmeterol xinafoate as the bronchodilator. Advair HFA is a pressurized metered-dose aerosol inhalers intended for oral inhalation. Advair HFA is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older. The usual dosage of Advair HFA is 2 inhalations twice a day. In contrast, the currently marketed Advair Diskus has the same indication as Advair HFA, but it is for use in patients age 4 and older, and the usual dosage is 1 inhalation twice a day. Neither product is indicated for the relief of acute bronchospasms.

For Advair HFA, it is recommended to prime the inhaler before using it for the first time, and in cases where the inhaler has not be used for more than four weeks, by releasing four test sprays into the air, away from the face. To maintain proper use of this product, the actuator should be washed and dried thoroughly at least once a week in order to prevent medication build-up. Advair HFA is supplied as a pressurized aluminum canister with a purple plastic actuator and light purple cap packaged together in a box with patient instructions. The canister is labeled with a net weight of 12 g and contains 120 metered inhalations. Advair HFA inhalation aerosol does not contain any chlorofluorocarbons (CFCs) as the propellant.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3,4</sup> for existing drug names which sound-alike or look-alike to Advair HFA to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5</sup>. The Saegis<sup>6</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving healthcare practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Advair HFA. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary name Advair HFA acceptable from a promotional perspective.
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Advair HFA. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Advair HFA	Fluticasone Propionate and Salmeterol Inhalation Aerosol 45 mcg/21 mcg per actuation, 115 mcg/21 mcg per actuation, and 230 mcg/21 mcg per actuation	Two oral inhalations twice a day.	N/A
Advair Diskus	Fluticasone Propionate and Salmeterol Inhalation Powder 100 mcg/50 mcg per actuation, 250 mcg/50 mcg per actuation, and 500 mcg/50 mcg per actuation	One oral inhalation twice a day.	LA/SA
Advicor	Lovastatin and Niacin Extended-release Tablets: 500 mg/20 mg, 750 mg/20 mg, and 1000 mg/20 mg	500 mg/20 mg, 1-2 tablets once daily.	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

<sup>1</sup> MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup>The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

<sup>4</sup> Phonetic and Orthographic Computer Analysis (POCA).

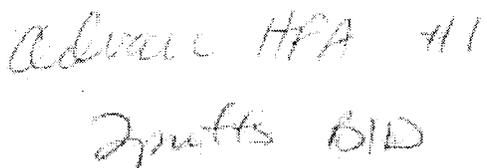
<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>6</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Advair HFA with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Advair HFA (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> 	<p>Advair HFA Dispense #1 Take 2 puffs twice a day</p>
<p><u>Inpatient RX:</u></p>	
<p><del>Advair HFA</del> <sup>Straker</sup> <del>well and install #1 puffs BID</del></p>	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed US product. See appendix A for the complete listing of the interpretations from the verbal and written studies.

## C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Advair Diskus has been marketed since August 24, 2000; thus, DMETS searched the FDA Adverse Event Reporting System (AERS) for all post-marketing safety reports of medication errors associated with the proprietary name Advair. The MedDRA Preferred Higher Level Group Term (HLGT) "Medication Errors" and verbatim substance name "Advair%" were used as search criteria. This search strategy retrieved seventy-five cases (75) involving Advair Diskus as follows:

- 43 cases pertained to overdoses.
- 17 cases pertained to confusion between Advair and Advicor.
- 11 cases pertained to confusion between the Advair strengths.
- 3 cases indicated that Advair was mistakenly dispensed, but the intended product was not disclosed. No additional information was provided in any of the cases.
- 1 case indicated that a patient received a placebo of Advair instead of Advair that contained medication. The patient's asthma symptoms worsened, but then resolved after the patient received Advair with active medication. No additional information was provided.

### 1. Overdose

For the forty-three cases pertaining to overdoses, the root causes are described below:

- Overdose: patients did not "feel" the medication when inhaled through the diskus and re-administered the dose (n=15).
- Wrong technique: patients pushed the lever twice before inhalation, resulting in additional doses (n=2)
- Lack of effect: patients did not feel Advair adequately relieved their symptoms so they used more than the prescribed dose (n=2)
- Diskus malfunction: multi-click fault-three blisters popped after each use (n=2), medication was not coming out of the diskus (n=1)
- Knowledge deficit: patient was not properly instructed on how to use the diskus or how many puffs to take after discharge from the hospital (n=1), patient thought the product had a propellant, thus kept loading the dose by pushing the lever (n=1), pt not sure if he received the full dose because the inhaler was almost empty (n=1)
- Unintentional overdoses: patient forgot she had already taken her dose(n=2)
- Medication was prescribed incorrectly by their practitioner: e.g. 2 puffs BID, 1 puff TID (n=5)
- Overdose: reason unknown, no additional information provided (n=11)

Adverse events that were reported as a result of the overdoses included tachycardia (3), hoarseness/cough (2), chest congestion (2), difficulty breathing (1), bloody nose (1), lightheadedness (1), edema (1), wheezing (1), hallucinations (1), and anxiety (1). Two patients who experienced tachycardia were seen in the emergency room, treated for their symptoms which then resolved. The events resolved for the patient who experienced a bloody nose, and the patient who experienced wheezing. The outcome is unknown for the remaining patients who experienced adverse events.

Given these errors above, DMETS recommends additional education on the proper use of the Advair Diskus in order to minimize future overdoses. Additionally, since Advair HFA will be a new formulation with different instructions for use, an educational campaign to inform practitioners and patients of the new dosage form will be instrumental in ensuring the proper use of each drug product.

## 2. Advair Diskus and Advicor name confusion

Seventeen cases pertained to confusion between Advair 500 mcg/50 mcg and Advicor 500 mg/20 mg. Fifteen cases were actual errors in which the wrong drug was dispensed and in two of these cases, the drug was administered. Reporters related the confusion between Advicor and Advair to orthographic similarities between the names and strengths. The two remaining cases cited practitioner concerns with the similarity of the names and strengths. No adverse reactions were reported. The outcome of the remaining cases is unknown. See section IID1(a) for further analysis of the Advair and Advicor errors.

## 3. Advair Diskus strength confusion

There were eleven cases of confusion between strengths of Advair Diskus. The most recent report was received in February 2006. Five cases involved confusion between the 250 mcg/50 mcg and 500 mcg/50 mcg strengths, one case described confusion between the 100 mcg/50 mcg and 500 mcg/50 mcg strengths, and three cases involved confusion between the 250 mcg/50 mcg and 100 mcg/50 mcg strengths. Adverse events such as difficulty breathing, asthma exacerbation, bronchitis, tachycardia, and decreased wound healing time were reported. The symptoms resolved for one patient that experienced difficulty breathing. The outcome is unknown in the remaining cases. Two cases specify that errors occurred between the Advair Diskus strengths because the labeling looks identical except for a small portion of the label that is differentiated by color (yellow, purple, and red). The specific strengths confused were not indicated for these two cases.

## D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Advair HFA, the primary concerns relating to potential look-alike and/or sound-alike confusion with Advair HFA were Advair Diskus and Advicor. DMETS also reviewed the potential for confusion with other HFA products. DMETS also reviewed post-marketing errors with Advair Diskus and has made recommendations in section III of this review that may help minimize similar confusion with Advair HFA.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Advair HFA could be confused with the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Advair HFA.

### 1. Existing and potential confusion with Advicor

- a. Post-marketing reports confirm confusion between Advicor and Advair (Diskus). Advicor is indicated for hypercholesterolemia and mixed dyslipidemia. It is a combination product containing niacin and lovastatin. Advicor is available as 500 mg/20 mg and 1000 mg/20 mg tablets. Advair Diskus is available as 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg powder for inhalation.

An AERS search revealed seventeen cases of confusion between Advicor 500 mg/20 mg and Advair [Diskus] 500 mcg/50 mcg. Fifteen cases resulted in the incorrect drug product reaching the patient, two of which were actually administered. No adverse reactions were reported. The outcome of the remaining cases is unknown. Eleven cases indicated that confusion occurred with written prescriptions, and one report indicated that a selection error occurred. DMETS cannot ascertain the specific cause of the errors from the remaining

cases aside from the reporters' indication of illegible handwriting, and to name and strength similarity of Advair and Advicor.

Both names contain 6 letters, begin with "Adv-", and end with the letter "r". Furthermore, Advair was approved in August 2000 and Advicor was approved in December 2001. Although some errors may have occurred due to both products being launched in close proximity, some errors occurred long after the launch. Advair and Advicor are combination drug products that share an overlapping numerator strength (Advair 500 mcg/50 mcg and Advicor 500 mg/20 mg), and the denominator strength may look similar when scripted (50 mcg vs. 20 mg).

Advicor 500/20  
Advair 500/50

These similarities are contributing factors of the errors between Advair and Advicor. DMETS noted the potential for confusion in our pre-marketing name review for Advicor (ODS consult 01-0165 dated August 21, 2001). However, at the time of that review, we searched AERS for any confusion between oral inhalers and solid oral dosage forms. The search resulted in zero cases of confusion. Therefore, we did not have any objections to the proprietary name, Advicor. DMETS notes that Advair [Diskus] is available in three strengths (100 mcg/50 mcg, 250 mcg/50 mcg, 500 mcg/50 mcg) and Advicor is available in two strengths (500 mg/20 mg and 1000 mg/20 mg). Yet, the medication errors between Advair and Advicor have occurred only between Advair 500 mcg/50 mcg and Advicor 500 mg/20 mg. The similarity of the names and the overlapping numerator strength contributes to the confusion between these two drug products. Since Advicor was the most recently approved drug product, a post-marketing review will be forwarded to your Division and to the Division of Metabolism and Endocrinology Products addressing these errors.

- b. Given the existing confusion between Advair [Diskus] and Advicor, we anticipate the potential for confusion upon introduction of Advair HFA. Advicor was identified as having look-alike similarities to Advair HFA if the modifier is omitted. Advicor and Advair HFA are both combination products that are administered orally. They share an overlapping usual dosage of (1 tab vs. 1 puff). Advicor and Advair HFA differ in indications for use (hypercholesterolemia vs. asthma), strength (500 mg/20 mg and 1000 mg/20 mg vs. 45 mcg/21 mcg, 115 mcg/21 mcg, 230 mcg/21 mcg), frequency of administration (once daily vs. twice a day), and dosage form (tablets vs. inhalation aerosol). Although errors have been reported between Advair Diskus and Advicor, the errors only occurred between the Advair 500 mcg/50 mcg and Advicor 500 mg/20 mg strengths. Thus, the root cause of the errors can be attributed to the similar names in conjunction with the overlapping numerator strengths and similar looking denominator strengths (500 mcg/50 mcg vs. 500 mg/20 mg). Even if the modifier is omitted from Advair HFA, DMETS believes that the potential for confusion between Advair HFA and Advicor might be minimized since Advair HFA does not share any overlapping numerical strengths with Advicor; although the denominators are similar (20 mg vs. 21 mcg), the numerator strengths are different (1000 mg vs. 115 mcg).

## 2. Advair Diskus and Advair HFA

Advair HFA is a product line extension of Advair Diskus. There is often confusion among different formulations because of the lack of knowledge that the new formulation exists. Advair Diskus and Advair HFA are combination products that contain the same active ingredients: fluticasone propionate and salmeterol. They also share the same indication for use, route of administration (oral inhalation), and frequency of administration (twice a day). Despite these similarities, the two drugs differ in strength (100 mcg/50 mcg, 250 mcg/50 mcg, 500 mcg/50 mcg vs. 45 mcg/21 mcg, 115 mcg/21 mcg, 230 mcg/21 mcg), usual dosage (1 inhalation vs. 2 inhalations), and dosage form (powder vs. aerosol). Additionally, Advair Diskus and Advair HFA possess different modifiers (Diskus vs. HFA). However, confusion between Advair Diskus and Advair HFA may occur if the modifiers are omitted, particularly for Advair 250 mcg/50 mcg and Advair 230 mcg/21 mcg due to their similar numerical numerator strengths. Currently, Advair is available in one formulation, thus, practitioners may omit the modifier (Diskus) on prescriptions and the patient will receive Advair Diskus. However, confusion may occur when Advair HFA is launched and a practitioner writes a prescription for "Advair 230 mcg/21 mcg" (omitting the modifier HFA). An error can occur primarily because a pharmacist may not be aware of the existence of the new dosage form and think that the practitioner made an error in writing the strength for Advair Diskus and dispense Advair Diskus. A patient may experience adverse events related to an overdose or underdose of medication if they are dispensed the incorrect product.

*Advair 250mcg/50mcg*  
*Advair 230mcg/21mcg*

*Advair 250/50*  
*Advair 230/21*

Post-marketing experience has shown when a new formulation of an existing drug product is launched, confusion and errors occur. Thus, it will be imperative to implement an extensive educational campaign to inform providers and patients about the differences between Advair HFA and Advair Diskus. Moreover, it is important that healthcare providers understand that Advair HFA is a new formulation, not just a new strength of Advair Diskus. Practitioners must be educated on how to switch patients from Advair Diskus to Advair HFA. In addition, it is likely that these products will be stored in close proximity on the pharmacy shelf. This may contribute to selection errors in a busy clinic, pharmacy or inpatient unit where the wrong product can be dispensed. It is important to distinguish Advair Diskus from Advair HFA. Thus, distinct labeling and extensive education are critical in order to minimize confusion between Advair Diskus and Advair HFA. The labeling, packaging, and product appearance can aid in the prevention of medication errors with Advair HFA and Advair Diskus. DMETS believes that the potential for confusion between the two formulations of Advair HFA is likely to occur, especially during the initial product launch, but can be minimized with unique labeling and packaging. The educational campaign must alert healthcare practitioners to the new dosage formulation including product differences such as dosing.

## 3. Other HFA products.

The following hydrofluoralkane (HFA) drug products are currently approved: Aerospan HFA, Atrovent HFA, Flovent HFA, Nasacort HFA, Proair HFA, Proventil HFA, Ventolin HFA, and Xopenex HFA. The aforementioned drug products contain hydrofluoralkane as the propellant. Since Advair HFA also contains hydrofluoralkane as the propellant, DMETS believes that the proprietary name Advair HFA is an appropriate name for this product as it also is consistent with the nomenclature used for currently marketed drug products.

5 Page(s) Withheld

       Trade Secret / Confidential

  /   Draft Labeling

       Deliberative Process

**Appendix A**  
 Prescription Study Results for Advair HFA

<b>Written Inpatient</b>	<b>Written Outpatient</b>	<b>Verbal</b>
Advair HFA	Advair HFA	Advair HFA
Advair HFA	Advair HFA	Advair HFA
Advair HFA	Advair HFA	Advair HFA
Advair HFA	Advair HFA	Advair HFA
Advair HFA	Advair HFA	Advair HFA
Advair HFA	Advair HFA	Advair HFA
Advair HFA	Advair HFA	Advair HFA
Advair HFA	Advair HFA	Advair HFA
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/s/

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